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(71) Applicant *(for all designated States except US)*: AXYS PHARMACEUTICALS, INC. [US/US]; 11099 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROOKS-WILSON, Angela, R. [CA/US]; 12685 Camino Mira Del Mar #145, San Diego, CA 92130 (US). BUCKLER, Alan [US/US]; 2315 Lagoon View Drive, Cardiff, CA 92007 (US). CARDON, Lon [US/US]; 12240 Katydid Circle, San Diego, CA 92129 (US). CAREY, Alisoun, H. [GB/US]; 3145 Galloway Drive, San Diego, CA 92122 (US). GALVIN, Margaret [US/US]; 7768 Corte Promenade, Carlsbad, CA 92009 (US). MILLER, Andrew [US/US]; 3717 Nobel Drive #1239, San Diego, CA 92122 (US). NORTH, Michael [GB/US]; 11099 North Torrey Pines Road, La Jolla, CA 92037 (US).

(74) Agent: SHERWOOD, Pamela, J.; Bozicevic, Field & Francis LLP, Suite 200, 285 Hamilton Avenue, Palo Alto, CA 94301 (US).

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(54) Title: ASTHMA RELATED GENES

(57) Abstract

A genetic locus associated with asthma is identified. The genes within the locus, *ASTH1I* and *ASTH1J*, and the regulatory sequences of the locus are characterized. The genes are used to produce the encoded proteins; in screening for compositions that modulate the expression or function of ASTH1 proteins; and in studying associated physiological pathways. The DNA is further used as a diagnostic for genetic predisposition to asthma.

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ASTHMA RELATED GENES

INTRODUCTION

Asthma is a disease of reversible bronchial obstruction, characterized by airway inflammation, epithelial damage, airway smooth muscle hypertrophy and bronchial hyperreactivity. Many asthma symptoms can be controlled by medical intervention, but incidence of asthma-related death and severe illness continue to rise in the United States. The approximately 4,800 deaths in 1989 marked a 46 percent increase since 1980. As many as 12 million people in the United States have asthma, up 66 percent since 1980, and annually, the disease's medical and indirect costs are estimated at over $6 billion.

Two common subdivisions of asthma are atopic (allergic, or extrinsic) asthma and non-atopic (intrinsic) asthma. Atopy is characterized by a predisposition to raise an IgE antibody response to common environmental antigens. In atopic asthma, asthma symptoms and evidence of allergy, such as a positive skin test to common allergens, are both present. Non-atopic asthma may be defined as reversible airflow limitation in the absence of allergies.

The smooth muscle surrounding the bronchi are able to rapidly alter airway diameter in response to stimuli. When the response is excessive, it is termed bronchial hyperreactivity, a characteristic of asthma thought to have a heritable component. Studies have demonstrated a genetic predisposition to asthma by showing, for example, a greater concordance for this trait among monozygotic twins than among dizygotic twins. The genetics of asthma is complex, however, and shows no simple pattern of inheritance. Environment also plays a role in asthma development, for example, children of smokers are more likely to develop asthma than are children of non-smokers.

In recent years thousands of human genes have been cloned. In many cases, gene discovery has been based on prior knowledge about the corresponding protein, such as amino acid sequence, immunological reactivity, *etc.* This approach has been very successful, but is limited in some important ways. One limitation is that genes in these cases are identified based on knowledge of molecular level protein properties. For a large number of important human genes, however, there

is little or no biochemical data concerning the encoded product. For example, genes that predispose to human diseases, such as cystic fibrosis, Huntington's disease, *etc.* are of interest because of their phenotypic effect. Biochemical characterization of such genes may be secondary to genetic characterization.

A solution to this impasse has been found in combining classical genetic mapping with the ability to identify genes and, if necessary, to sequence large regions of chromosomes. Population and family studies enable genes associated with a trait of interest to be localized to a relatively small region of a chromosome. At this point, physical mapping can be used to identify candidate genes, and various molecular biology techniques used to pick out mutated genes in affected individuals. This "top-down" approach to gene discovery has been termed positional cloning, because genes are identified based on position in the genome.

Positional cloning is now being applied to complex genetic diseases, which affect a greater fraction of humanity than do the more simple and usually rarer single gene disorders. Such studies must take into account the contribution of both environmental and genetic factors to the development of disease, and must allow for contributions to the genetic component by more than one, and potentially many, genes. The clinical importance of asthma makes it of considerable interest to characterize genes that underlie a genetic predisposition to this disease. Positional cloning provides an approach to this goal.

Relevant Literature

The symptoms and biology of asthma are reviewed in Chanez *et al.* (1994) Odyssey **1**:24-33. A review of bronchial hyperreactivity may be found in Smith and McFadden (1995) Ann. Allergy, Asthma and Immunol. **74**:454. Moss (1989) Annals of Allergy **63**:566 review the allergic etiology and immunology of asthma.

The genetic dissection of complex traits is discussed in Lander and Schork (1994) Science **265**:2037-2048. Genetic mapping of candidate genes for atopy and/or bronchial hyperreactivity is described in Postma *et al.* (1995) N.E.J.M. **333**:894; Marsh *et al.* (1994) Science **264**:1152; and Meyers *et al.* (1994) Genomics **23**:464.

Lawrence *et al.* (1994) Ann. Hum. Genet. **58**:359 discuss an approach to the genetic analysis of atopy and asthma. Genetic linkage between the alpha subunit of the T cell receptor and IgE reactions has been noted by Moffat *et al.* (1994) The Lancet 343:1597. Caraballo and Hernandez (1990) Tissue Antigens **35**:182 noted an association between HLA alleles and allergic asthma. Evidence of linkage of atopy to markers on chromosome 11q has been seen in some British asthma families (Cookson *et al.* (1989) Lancet **i**:1292-1295; Young *et al.* (1991) J. Med. Genet. **29**:236, but not in other British families (Lympany *et al.* (1992) Clin. Exp. Allergy **22**:1085-1092) or in families from Minnesota or Japan (Rich *et al.* (1992) Clin. Exp. Allergy **22**:1070-1076; and Hizawa *et al.* (1992) Clin. Exp. Allergy 22:1065).

The association of a polymorphism for the FcεRI-β gene and risk of atopy is described in Hill *et al.* (1995) B.M.J. **311**:776; Hill and Cookson (1996) Human Mol. Genet. **5**:959; and Shirakawa *et al.* (1994) Nature Genetics **7**:125; an association of FcεRI-β with bronchial hyperreactivity is described in van Herwerden (1995) The Lancet **346**:1262.

Collections of polymorphic markers from throughout the human genome have been tested for linkage to asthma, described in Meyers *et al.* (1996) Am. J. Hum. Genet. **59**:A228 and Daniels *et al.* (1996) Nature **383**:247-250. No linkage to human chromosome 11p was detected in these studies.

SUMMARY OF THE INVENTION

Human genes associated with a genetic predisposition to asthma are provided. The genes, herein termed *ASTH1I* and *ASTH1J*, are located close to each other on human chromosome 11p, have similar patterns of expression, and common sequence motifs. The nucleic acid compositions are used to produce the encoded proteins, which may be employed for functional studies, as a therapeutic, and in studying associated physiological pathways. The nucleic acid compositions and antibodies specific for the protein are useful as diagnostics to identify a hereditary predisposition to asthma.

Brief Description of the Drawings

Figure 1: Genomic organization of the *ASTH*1I and *ASTH*1J genes. The sizes of the exons are not to scale. Alternative exons are hatched. The direction of transcription is indicated below each gene.

Description of the Specific Embodiments

The provided *ASTH1* genes and fragments thereof, encoded protein, *ASTH1* genomic regulatory regions, and anti-*ASTH*1 antibodies are useful in the identification of individuals predisposed to development of asthma, and for the modulation of gene activity *in vivo* for prophylactic and therapeutic purposes. The encoded *ASTH*1 protein is useful as an immunogen to raise specific antibodies, in drug screening for compositions that mimic or modulate *ASTH*1 activity or expression, including altered forms of *ASTH*1 protein, and as a therapeutic.

Asthma, as defined herein, is reversible airflow limitation in a patient over a period of time. The disease is characterized by increased airway responsiveness to a variety of stimuli, and airway inflammation. A patient diagnosed as asthmatic will generally have multiple indications over time, including wheezing, asthmatic attacks, and a positive response to methacholine challenge, *i.e.* a PC_{20} on methacholine challenge of less than about 4 mg/ml. Guidelines for diagnosis may be found in the <u>National Asthma Education Program Expert Panel. Guidelines for diagnosis and management of asthma</u>. National Institutes of Health, 1991; Pub. #91-3042. Atopy, respiratory infection and environmental predisposing factors may also be present, but are not necessary elements of an asthma diagnosis. Asthma conditions strictly related to atopy are referred to as atopic asthma.

The human *ASTH1I* and *ASTH1J* gene sequences are provided, as are the genomic sequences 5' to *ASTH1J*. The major sequences of interest provided in the sequence listing are as follows:

ASTH1J 5' Genomic Region	DNA	(SEQ ID NO:1)
ASTH1J alt1	cDNA	(SEQ ID NO:2)
ASTH1J alt2	cDNA	(SEQ ID NO:3)
ASTH1J alt3	cDNA	(SEQ ID NO:4)

ASTH1J protein	protein	(SEQ ID NO:5)
ASTH1I alt1	cDNA	(SEQ ID NO:6)
ASTH1I alt1 protein	protein	(SEQ ID NO:7)
ASTH1I alt2	cDNA	(SEQ ID NO:8)
ASTH1I alt2 protein	protein	(SEQ ID NO:9)
ASTH1I alt3	cDNA	(SEQ ID NO:10)
ASTH1I alt3 protein	protein	(SEQ ID NO:11)
CAAT box "A" form	DNA	(SEQ ID NO:12)
CAAT box "G" form	DNA	(SEQ ID NO:13)
ASTH1J 5' promoter region	DNA	(SEQ ID NO:14)
Mouse *asth1j*	cDNA	(SEQ ID NO:338)
Mouse asth1j	protein	(SEQ ID NO:339)
Polymorphisms	DNA	(SEQ ID NO:16-159)
Microsatellite flanking sequences	DNA	(SEQ ID NO:160-281)
Microsatellite repeats	DNA	(SEQ ID NO:282-292)
Intron-Exon boundaries	DNA	(SEQ ID NO:293-335)

The *ASTH1* locus has been mapped to human chromosome 11p. The traits for a positive response to methacholine challenge and a clinical history of asthma were shown to be genetically linked in a genome scan of the population of Tristan da Cunha, a single large extended family with a high incidence of asthma (discussed in Zamel *et al.* (1996) Am. J. Respir. Crit. Care Med. **153**:1902-1906). The linkage finding was replicated in a set of Canadian asthmatic families. The region of strongest linkage was the marker D11S907 on the short arm of chromosome 11. Additional markers were identified from the four megabase region surrounding D11S907 from public databases and by original cloning of new polymorphic microsatellite markers. Refinement of the region of interest was obtained by genotyping new markers in the studied populations, and applying the transmission disequilibrium test (TDT), which reflects the level of association between marker alleles and disease status. TDT curves were superimposed on the

physical map. Molecular genetic techniques for gene identification were applied to the region of interest. A one megabase genomic region was sequenced to high accuracy, and the resulting data used for the sequence-based prediction of gen s and determination of the intron/exon structure of genes in the region.

Nucleic Acid Compositions

ASTH1I produces a 2.8 kb mRNA expressed at high levels in trachea and prostate, and at lower levels in lung and kidney and possibly other tissues. ASTH1I cDNA clones have also been identified in prostate, testis and lung libraries. Sequence polymorphisms are shown in Table 3. ASTH1I has at least three alternate forms denoted as alt1, alt2, and alt3. The alternative splicing and start codons give the three forms of ASTH1I proteins different amino termini. The ASTH1I proteins, alt1, alt2 and alt3 are 265, 255 and 164 amino acids in length, respectively.

A domain of the ASTH1I and ASTH1J proteins is similar in sequence to transcription factors of the *ets* family. The *ets* family is a group of transcription factors that activate genes involved in a variety of immunological and other processes. The family members most similar to ASTH1I and ASTH1J are: ETS1, ETS2, ESX, ELF, ELK1, TEL, NET, SAP-1, NERF and FLI. The ASTH1I and ASTH1J proteins show similarity to each other. Over the *ets* domain they are 66% similar (*ie.* have amino acids with similar properties in the same positions) and 46% identical to each other. All forms of ASTH1I and ASTH1J have a helix turn helix motif, characteristic of some transcription factors, located near the carboxy terminal end of the protein.

ASTH1J produces an approximately 6 kb mRNA expressed at high levels in the trachea, prostate and pancreas and at lower levels in colon, small intestine, lung and stomach. *ASTH1J* has at least three forms, consisting of the alt1, alt2 and alt3 forms. The open reading frame is identical for the three forms, which differ only in the 5' UTR. The protein encoded by ASTH1J is 300 amino acids in length.

Mouse coding region sequence of *asth1j* is provided in SEQ ID NO:326, and the amino acid sequence is provided in SEQ ID NO:327. The mouse and human proteins have 88.4% identity throughout their length. The match in the *ets*

domain is 100%. The mouse cDNA was identified by hybridization of a full-length human cDNA to a mouse lung cDNA library (Stratagene).

The term "*ASTH1* genes" is herein used generically to designate *ASTH1I* and *ASTH1J* genes and their alternate forms. The two genes lie in opposite orientations on a native chromosome, with the 5' regulatory sequences between them. Part of the genomic sequence between the two coding regions is provided as SEQ ID NO:1. The term "*ASTH1* locus" is used herein to refer to the two genes in all alternate forms and the genomic sequence that lies between the two genes. Alternate forms include splicing variants, and polymorphisms in the sequence. Specific polymorphic sequences are provided in SEQ ID NOs:16-159. For some purposes the previously known EST sequences described herein may be excluded from the sequences defined as the ASTH1 locus.

The DNA sequence encoding ASTH1 may be cDNA or genomic DNA or a fragment thereof. The term "*ASTH1* gene" shall be intended to mean the open reading frame encoding specific ASTH1 polypeptides, introns, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 1 kb beyond the coding region, but possibly further in either direction. The gene may be introduced into an appropriate vector for extrachromosomal maintenance or for integration into the host.

The term "cDNA" as used herein is intended to include all nucleic acids that share the arrangement of sequence elements found in native mature mRNA species, where sequence elements are exons and 3' and 5' non-coding regions. Normally mRNA species have contiguous exons, with the intervening introns removed by nuclear RNA splicing, to create a continuous open reading frame encoding the ASTH1 protein.

The genomic *ASTH1* sequence has non-contiguous open reading frames, where introns interrupt the protein coding regions. A genomic sequence of interest comprises the nucleic acid present between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It may further include the 3' and 5' untranslated regions found in the mature mRNA. It may further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, *etc.*,

including about 1 kb, but possibly more, of flanking genomic DNA at either the 5' or 3' end of the transcribed region. The genomic DNA may be isolated as a fragment of 100 kbp or smaller; and substantially free of flanking chromosomal sequence.

Genomic regions of interest include the non-transcribed sequences 5' to *ASTH1J*, as provided in SEQ ID NO:1. This region of DNA contains the native promoter elements that direct expression of the linked *ASTH1J* gene. Usually a promoter region will have at least about 140 nt of sequence located 5' to the *ASTH1* gene and further comprising a TATA box and CAAT box motif sequence (SEQ ID NO:14, nt. 597-736). The promoter region may further comprise a consensus *ets* binding motif, (C/A)GGA(A/T) (SEQ ID NO:14, nt 1-5). A region of particular interest, containing the *ets* binding motif, TATA box and CAAT box motifs 5' to the *ASTH1J* gene, is provided in SEQ ID NO:14. The position of SEQ ID NO:14 within the larger sequence is SEQ ID NO:1, nt 60359-61095. The promoter sequence may comprise polymorphisms within the CAAT box region, for example those shown in SEQ ID NO:12 and SEQ ID NO:13, which have been shown to affect the function of the promoter. The promoter region of interest may extend 5' to SEQ ID NO:14 within the larger sequence, *e.g.* SEQ ID NO:1, nt 59000-61095; SEQ ID NO:1, nt 5700-61095, *etc.*

The sequence of this 5' region, and further 5' upstream sequences and 3' downstream sequences, may be utilized for promoter elements, including enhancer binding sites, that provide for expression in tissues where *ASTH1J* is expressed. The tissue specific expression is useful for determining the pattern of expression, and for providing promoters that mimic the native pattern of expression. Naturally occurring polymorphisms in the promoter region are useful for determining natural variations in expression, particularly those that may be associated with disease. See, for example, SEQ ID NO:12 and 13. Alternatively, mutations may be introduced into the promoter region to determine the effect of altering expression in experimentally defined systems. Methods for the identification of specific DNA motifs involved in the binding of transcriptional factors are known in the art, *e.g.* sequence similarity to known binding motifs, gel retardation studies, *etc.* For examples, see Blackwell *et al.* (1995) Mol Med 1: 194-205; Mortlock *et al.* (1996)

Genome Res. **6**: 327-33; and Joulin and Richard-Foy (1995) Eur J Biochem **232**: 620-626.

The regulatory sequences may be used to identify *cis* acting sequences required for transcriptional or translational regulation of ASTH1 expression, especially in different tissues or stages of development, and to identify *cis* acting sequences and *trans* acting factors that regulate or mediate ASTH1 expression. Such transcription or translational control regions may be operably linked to a ASTH1 gene in order to promote expression of wild type or altered ASTH1 or other proteins of interest in cultured cells, or in embryonic, fetal or adult tissues, and for gene therapy.

The nucleic acid compositions of the subject invention may encode all or a part of the subject polypeptides. Fragments may be obtained of the DNA sequence by chemically synthesizing oligonucleotides in accordance with conventional methods, by restriction enzyme digestion, by PCR amplification, *etc.* For the most part, DNA fragments will be of at least 15 nt, usually at least 18 nt, more usually at least about 50 nt. Such small DNA fragments are useful as primers for PCR, hybridization screening, *etc.* Larger DNA fragments, *i.e.* greater than 100 nt are useful for production of the encoded polypeptide. For use in amplification reactions, such as PCR, a pair of primers will be used. The exact composition of the primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject sequence under stringent conditions, as known in the art. It is preferable to choose a pair of primers that will generate an amplification product of at least about 50 nt, preferably at least about 100 nt. Algorithms for the selection of primer sequences are generally known, and are available in commercial software packages. Amplification primers hybridize to complementary strands of DNA, and will prime towards each other.

The *ASTH1* genes are isolated and obtained in substantial purity, generally as other than an intact mammalian chromosome. Usually, the DNA will be obtained substantially free of other nucleic acid sequences that do not include an *ASTH1* sequence or fragment thereof, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant", *i.e.* flanked by one or more

nucleotides with which it is not normally associated on a naturally occurring chromosome.

The DNA sequences are used in a variety of ways. They may be used as probes for identifying *ASTH1* related genes. Mammalian homologs have substantial sequence similarity to the subject sequences, *i.e.* at least 75%, usually at least 90%, more usually at least 95% sequence identity with the nucleotide sequence of the subject DNA sequence. Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as a conserved motif, coding region, flanking region, *etc.* A reference sequence will usually be at least about 18 nt long, more usually at least about 30 nt long, and may extend to the complete sequence that is being compared. Algorithms for sequence analysis are known in the art, such as BLAST, described in Altschul *et al.* (1990) J Mol Biol **215**:403-10.

Nucleic acids having sequence similarity are detected by hybridization under low stringency conditions, for example, at 50°C and 10XSSC (0.9 M saline/0.09 M sodium citrate) and remain bound when subjected to washing at 55°C in 1XSSC. Sequence identity may be determined by hybridization under stringent conditions, for example, at 50°C or higher and 0.1XSSC (9 mM saline/0.9 mM sodium citrate). By using probes, particularly labeled probes of DNA sequences, one can isolate homologous or related genes. The source of homologous genes may be any species, *e.g.* primate species, particularly human; rodents, such as rats and mice, canines, felines, bovines, ovines, equines, yeast, *Drosophila*, *Caenhorabditis*, *etc.*

The DNA may also be used to identify expression of the gene in a biological specimen. The manner in which one probes cells for the presence of particular nucleotide sequences, as genomic DNA or RNA, is well established in the literature and does not require elaboration here. mRNA is isolated from a cell sample. mRNA may be amplified by RT-PCR, using reverse transcriptase to form a complementary DNA strand, followed by polymerase chain reaction amplification using primers specific for the subject DNA sequences. Alternatively, mRNA sample is separated by gel electrophoresis, transferred to a suitable support, *e.g.* nitrocellulose, nylon, *etc.*, and then probed with a fragment of the subject DNA as a probe. Other techniques, such as oligonucleotide ligation assays, *in situ*

hybridizations, and hybridization to DNA probes arrayed on a solid chip may also find use. Detection of mRNA hybridizing to the subject sequence is indicative of *ASTH1* gene expression in the sample.

The subject nucleic acid sequences may be modified for a number of purposes, particularly where they will be used intracellularly, for example, by being joined to a nucleic acid cleaving agent, *e.g.* a chelated metal ion, such as iron or chromium for cleavage of the gene; or the like.

The sequence of the *ASTH1* locus, including flanking promoter regions and coding regions, may be mutated in various ways known in the art to generate targeted changes in promoter strength, sequence of the encoded protein, *etc.* The DNA sequence or product of such a mutation will be substantially similar to the sequences provided herein, *i.e.* will differ by at least one nucleotide or amino acid, respectively, and may differ by at least two but not more than about ten nucleotides or amino acids. The sequence changes may be substitutions, insertions or deletions. Deletions may further include larger changes, such as deletions of a domain or exon. Other modifications of interest include epitope tagging, *e.g.* with the FLAG system, HA, *etc.* For studies of subcellular localization, fusion proteins with green fluorescent proteins (GFP) may be used. Such mutated genes may be used to study structure-function relationships of ASTH1 polypeptides, or to alter properties of the protein that affect its function or regulation. For example, constitutively active transcription factors, or a dominant negatively active protein that binds to the ASTH1 DNA target site without activating transcription, may be created in this manner.

Techniques for *in vitro* mutagenesis of cloned genes are known. Examples of protocols for scanning mutations may be found in Gustin *et al.*, *Biotechniques* 14:22 (1993); Barany, *Gene* 37:111-23 (1985); Colicelli *et al.*, *Mol Gen Genet* 199:537-9 (1985); and Prentki *et al.*, *Gene* 29:303-13 (1984). Methods for site specific mutagenesis can be found in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp. 15.3-15.108; Weiner *et al., Gene* 126:35-41 (1993); Sayers *et al.*, *Biotechniques* 13:592-6 (1992); Jones and Winistorfer, *Biotechniques* 12:528-30 (1992); Barton *et al.*, *Nucleic Acids Res* 18:7349-55

(1990); Marotti and Tomich, *Gene Anal Tech* 6:67-70 (1989); and *Zhu Anal Biochem* 177:120-4 (1989).

Synthesis of ASTH1 Proteins

The subject gene may be employed for synthesis of a complete ASTH1 protein, or polypeptide fragments thereof, particularly fragments corresponding to functional domains; binding sites; *etc.*; and including fusions of the subject polypeptides to other proteins or parts thereof. For expression, an expression cassette may be employed, providing for a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. Various transcriptional initiation regions may be employed that are functional in the expression host.

The polypeptides may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli, B. subtilis, S. cerevisiae*, or cells of a higher organism such as vertebrates, particularly mammals, *e.g.* COS 7 cells, may be used as the expression host cells. In many situations, it may be desirable to express the *ASTH1* gene in mammalian cells, where the *ASTH1* gene will benefit from native folding and post-translational modifications. Small peptides can also be synthesized in the laboratory.

With the availability of the polypeptides in large amounts, by employing an expression host, the polypeptides may be isolated and purified in accordance with conventional ways. A lysate may be prepared of the expression host and the lysate purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. The purified polypeptide will generally be at least about 80% pure, preferably at least about 90% pure, and may be up to and including 100% pure. Pure is intended to mean free of other proteins, as well as cellular debris.

The polypeptide is used for the production of antibodies, where short fragments provide for antibodies specific for the particular polypeptide, and larger fragments or the entire protein allow for the production of antibodies over the surface of the polypeptide. Antibodies may be raised to the wild-type or variant

forms of ASTH1. Antibodies may be raised to isolated peptides corresponding to these domains, or to the native protein, *e.g.* by immunization with cells expressing ASTH1, immunization with liposomes having ASTH1 inserted in the membrane, *etc.*

Antibodies are prepared in accordance with conventional ways, where the expressed polypeptide or protein is used as an immunogen, by itself or conjugated to known immunogenic carriers, *e.g.* KLH, pre-S HBsAg, other viral or eukaryotic proteins, or the like. Various adjuvants may be employed, with a series of injections, as appropriate. For monoclonal antibodies, after one or more booster injections, the spleen is isolated, the lymphocytes immortalized by cell fusion, and then screened for high affinity antibody binding. The immortalized cells, *i.e.* hybridomas, producing the desired antibodies may then be expanded. For further description, see Monoclonal Antibodies: A Laboratory Manual, Harlow and Lane eds., Cold Spring Harbor Laboratories, Cold Spring Harbor, New York, 1988. If desired, the mRNA encoding the heavy and light chains may be isolated and mutagenized by cloning in *E. coli*, and the heavy and light chains mixed to further enhance the affinity of the antibody. Alternatives to *in vivo* immunization as a method of raising antibodies include binding to phage "display" libraries, usually in conjunction with *in vitro* affinity maturation.

Detection of ASTH1 Associated Asthma

Diagnosis of ASTH1 associated asthma is performed by protein, DNA or RNA sequence and/or hybridization analysis of any convenient sample from a patient, *e.g.* biopsy material, blood sample, scrapings from cheek, *etc.* A nucleic acid sample from a patient having asthma that may be associated with *ASTH1*, is analyzed for the presence of a predisposing polymorphism in *ASTH1*. A typical patient genotype will have at least one predisposing mutation on at least one chromosome. The presence of a polymorphic *ASTH1* sequence that affects the activity or expression of the gene product, and confers an increased susceptibility to asthma is considered a predisposing polymorphism. Individuals are screened by analyzing their DNA or mRNA for the presence of a predisposing polymorphism, as compared to an asthma neutral sequence. Specific sequences of interest include any polymorphism that leads to clinical bronchial hyperreactivity or is otherwise associated with asthma, including, but not limited to, insertions, substitutions and

deletions in the coding region sequence, intron sequences that affect splicing, or promoter or enhancer sequences that affect the activity and expression of the protein. Examples of specific *ASTH1* polymorphisms in asthma patients are listed in Tables 3-8.

The CAAT box polymorphism of SEQ ID NO:12 and 13 (which is located within SEQ ID NO:14) is of particular interest. The "G" form, SEQ ID NO:13, can be associated with a propensity to develop bronchial hyperreactivity or asthma. Other polymorphisms in the surrounding region affect this association. It has been found that substitution of "G" for "A" results in decreased binding of nuclear proteins to the DNA motif.

The effect of an ASTH1 predisposing polymorphism may be modulated by the patient genotype in other genes related to asthma and atopy, including, but not limited to, the Fcε receptor, Class I and Class II HLA antigens, T cell receptor and immunoglobulin genes, cytokines and cytokine receptors, and the like.

Screening may also be based on the functional or antigenic characteristics of the protein. Immunoassays designed to detect predisposing polymorphisms in ASTH1 proteins may be used in screening. Where many diverse mutations lead to a particular disease phenotype, functional protein assays have proven to be effective screening tools.

Biochemical studies may be performed to determine whether a candidate sequence polymorphism in the *ASTH1* coding region or control regions is associated with disease. For example, a change in the promoter or enhancer sequence that affects expression of *ASTH1* may result in predisposition to asthma. Expression levels of a candidate variant allele are compared to expression levels of the normal allele by various methods known in the art. Methods for determining promoter or enhancer strength include quantitation of the expressed natural protein; insertion of the variant control element into a vector with a reporter gene such as β–galactosidase, luciferase, chloramphenicol acetyltransferase, *etc.* that provides for convenient quantitation; and the like. The activity of the encoded ASTH1 protein may be determined by comparison with the wild-type protein.

A number of methods are available for analyzing nucleic acids for the presence of a specific sequence. Where large amounts of DNA are available, genomic DNA is used directly. Alternatively, the region of interest is cloned into a suitable vector and grown in sufficient quantity for analysis. Cells that express *ASTH1* genes, such as trachea cells, may be used as a source of mRNA, which may be assayed directly or reverse transcribed into cDNA for analysis. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki, *et al.* (1985) Science **239**:487, and a review of current techniques may be found in Sambrook, *et al.* Molecular Cloning: A Laboratory Manual, CSH Press 1989, pp.14.2–14.33. Amplification may also be used to determine whether a polymorphism is present, by using a primer that is specific for the polymorphism. Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms, for examples see Riley *et al.* (1990) N.A.R. **18**:2887-2890; and Delahunty *et al.* (1996) Am. J. Hum. Genet. **58**:1239-1246.

A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, *e.g.* fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein (6-FAM), 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2',4',7',4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA), radioactive labels, *e.g.* ^{32}P, ^{35}S, ^{3}H; *etc.* The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, *etc.* having a high affinity binding partner, *e.g.* avidin, specific antibodies, *etc.*, where the binding partner is conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

The sample nucleic acid, *e.g.* amplified or cloned fragment, is analyzed by one of a number of methods known in the art. The nucleic acid may be sequenced by dideoxy or other methods, and the sequence of bases compared to a neutral *ASTH1* sequence. Hybridization with the variant sequence may also be used to

determine its presence, by Southern blots, dot blots, *etc.* The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilised on a solid support, as described in US 5,445,934, or in WO95/35505, may also be used as a means of detecting the presence of variant sequences. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), mismatch cleavage detection, and heteroduplex analysis in gel matrices are used to detect conformational changes created by DNA sequence variation as alterations in electrophoretic mobility. Alternatively, where a polymorphism creates or destroys a recognition site for a restriction endonuclease (restriction fragment length polymorphism, RFLP), the sample is digested with that endonuclease, and the products size fractionated to determine whether the fragment was digested. Fractionation is performed by gel or capillary electrophoresis, particularly acrylamide or agarose gels.

The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilised on a solid support, as described in US 5,445,934, or in WO95/35505, may be used as a means of detecting the presence of variant sequences. In one embodiment of the invention, an array of oligonucleotides are provided, where discrete positions on the array are complementary to at least a portion of mRNA or genomic DNA of the *ASTH1* locus. Such an array may comprise a series of oligonucleotides, each of which can specifically hybridize to a nucleic acid, *e.g.* mRNA, cDNA, genomic DNA, *etc.* from the *ASTH1* locus.

An array may include all or a subset of the polymorphisms listed in Table 3 (SEQ ID NOs:16-126). One or both polymorphic forms may be present in the array, for example the polymorphism of SEQ ID NO:12 and 13 may be represented by either, or both, of the listed sequences. Usually such an array will include at least 2 different polymorphic sequences, *i.e.* polymorphisms located at unique positions within the locus, usually at least about 5, more usually at least about 10, and may include as many as 50 to 100 different polymorphisms. The oligonucleotide sequence on the array will usually be at least about 12 nt in length, may be the length of the provided polymorphic sequences, or may extend into the flanking regions to generate fragments of 100 to 200 nt in length. For examples of arrays,

see Hacia *et al.* (1996) Nature Genetics **14**:441-447; Lockhart *et al.* (1996) Nature Biotechnol. **14**:1675-1680; and De Risi *et al.* (1996) Nature Genetics **14**:457-460.

Antibodies specific for ASTH1 polymorphisms may be used in screening immunoassays. A reduction or increase in neutral ASTH1 and/or presence of asthma associated polymorphisms is indicative that asthma is ASTH1-associated. A sample is taken from a patient suspected of having ASTH1-associated asthma. Samples, as used herein, include biological fluids such as tracheal lavage, blood, cerebrospinal fluid, tears, saliva, lymph, dialysis fluid and the like; organ or tissue culture derived fluids; and fluids extracted from physiological tissues. Also included in the term are derivatives and fractions of such fluids. Biopsy samples are of particular interest, *e.g.* trachea scrapings, *etc.* The number of cells in a sample will generally be at least about 10^3, usually at least 10^4 more usually at least about 10^5. The cells may be dissociated, in the case of solid tissues, or tissue sections may be analyzed. Alternatively a lysate of the cells may be prepared.

Diagnosis may be performed by a number of methods. The different methods all determine the absence or presence or altered amounts of normal or abnormal ASTH1 in patient cells suspected of having a predisposing polymorphism in ASTH1. For example, detection may utilize staining of cells or histological sections, performed in accordance with conventional methods. The antibodies of interest are added to the cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, a second stage antibody or reagent is used to amplify the signal. Such reagents are well known in the art. For example, the primary antibody may be conjugated to biotin, with horseradish peroxidase-conjugated avidin added as a second stage reagent. Final detection uses a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding may be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, scintillation counting, *etc.*

An alternative method for diagnosis depends on the *in vitro* detection of binding between antibodies and ASTH1 in a lysate. Measuring the concentration of

ASTH1 binding in a sample or fraction thereof may be accomplished by a variety of specific assays. A conventional sandwich type assay may be used. For example, a sandwich assay may first attach ASTH1-specific antibodies to an insoluble surface or support. The particular manner of binding is not crucial so long as it is compatible with the reagents and overall methods of the invention. They may be bound to the plates covalently or non-covalently, preferably non-covalently.

The insoluble supports may be any compositions to which polypeptides can be bound, which is readily separated from soluble material, and which is otherwise compatible with the overall method. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports to which the receptor is bound include beads, *e.g.* magnetic beads, membranes and microtiter plates. These are typically made of glass, plastic (*e.g.* polystyrene), polysaccharides, nylon or nitrocellulose. Microtiter plates are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples.

Patient sample lysates are then added to separately assayable supports (for example, separate wells of a microtiter plate) containing antibodies. Preferably, a series of standards, containing known concentrations of normal and/or abnormal ASTH1 is assayed in parallel with the samples or aliquots thereof to serve as controls. Preferably, each sample and standard will be added to multiple wells so that mean values can be obtained for each. The incubation time should be sufficient for binding, generally, from about 0.1 to 3 hr is sufficient. After incubation, the insoluble support is generally washed of non-bound components. Generally, a dilute non-ionic detergent medium at an appropriate pH, generally 7-8, is used as a wash medium. From one to six washes may be employed, with sufficient volume to thoroughly wash non-specifically bound proteins present in the sample.

After washing, a solution containing a second antibody is applied. The antibody will bind ASTH1 with sufficient specificity such that it can be distinguished from other components present. The second antibodies may be labeled to facilitate direct, or indirect quantification of binding. Examples of labels that permit direct measurement of second receptor binding include radiolabels, such as ^{3}H or ^{125}I, fluorescers, dyes, beads, chemilumninescers, colloidal particles, and the like.

Examples of labels which permit indirect measurement of binding include enzymes where the substrate may provide for a colored or fluorescent product. In a preferred embodiment, the antibodies are labeled with a covalently bound enzyme capable of providing a detectable product signal after addition of suitable substrate. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art. The incubation time should be sufficient for the labeled ligand to bind available molecules. Generally, from about 0.1 to 3 hr is sufficient, usually 1 hr sufficing.

After the second binding step, the insoluble support is again washed free of non-specifically bound material. The signal produced by the bound conjugate is detected by conventional means. Where an enzyme conjugate is used, an appropriate enzyme substrate is provided so a detectable product is formed.

Other immunoassays are known in the art and may find use as diagnostics. Ouchterlony plates provide a simple determination of antibody binding. Western blots may be performed on protein gels or protein spots on filters, using a detection system specific for ASTH1 as desired, conveniently using a labeling method as described for the sandwich assay.

Other diagnostic assays of interest are based on the functional properties of ASTH1 proteins. Such assays are particularly useful where a large number of different sequence changes lead to a common phenotype, *i.e.* altered protein function leading to bronchial hyperreactivity. For example, a functional assay may be based on the transcriptional changes mediated by *ASTH1* gene products. Other assays may, for example, detect conformational changes, size changes resulting from insertions, deletions or truncations, or changes in the subcellular localization of ASTH1 proteins.

In a protein truncation test, PCR fragments amplified from the *ASTH1* gene or its transcript are used as templates for *in vivo* transcription/translation reactions to generate protein products. Separation by gel electrophoresis is performed to determine whether the polymorphic gene encodes a truncated protein, where truncations may be associated with a loss of function.

Diagnostic screening may also be performed for polymorphisms that are genetically linked to a predisposition for bronchial hyperreactivity, particularly through the use of microsatellite markers or single nucleotide polymorphisms. Frequently the microsatellite polymorphism itself is not phenotypically expressed, but is linked to sequences that result in a disease predisposition. However, in some cases the microsatellite sequence itself may affect gene expression. Microsatellite linkage analysis may be performed alone, or in combination with direct detection of polymorphisms, as described above. The use of microsatellite markers for genotyping is well documented. For examples, see Mansfield *et al.* (1994) Genomics 24:225-233; Ziegle *et al.* (1992) Genomics 14:1026-1031; Dib *et al., supra.*

Microsatellite loci that are useful in the subject methods have the general formula:

$$U\ (R)_n\ U', \text{ where}$$

U and U' are non-repetitive flanking sequences that uniquely identify the particular locus, R is a repeat motif, and n is the number of repeats. The repeat motif is at least 2 nucleotides in length, up to 7, usually 2-4 nucleotides in length. Repeats can be simple or complex. The flanking sequences U and U' uniquely identify the microsatellite locus within the human genome. U and U' are at least about 18 nucleotides in length, and may extend several hundred bases up to about 1 kb on either side of the repeat. Within U and U', sequences are selected for amplification primers. The exact composition of the primer sequences are not critical to the invention, but they must hybridize to the flanking sequences U and U', respectively, under stringent conditions. Criteria for selection of amplification primers are as previously discussed. To maximize the resolution of size differences at the locus, it is preferable to chose a primer sequence that is close to the repeat sequence, such that the total amplification product is between 100-500 nucleotides in length.

The number of repeats at a specific locus, n, is polymorphic in a population, thereby generating individual differences in the length of DNA that lies between the amplification primers. The number will vary from at least 1 repeat to as many as about 100 repeats or more.

The primers are used to amplify the region of genomic DNA that contains the repeats. Conveniently, a detectable label will be included in the amplification reaction, as previously described. Multiplex amplification may be performed in which several sets of primers are combined in the same reaction tube. This is particularly advantageous when limited amounts of sample DNA are available for analysis. Conveniently, each of the sets of primers is labeled with a different fluorochrome.

After amplification, the products are size fractionated. Fractionation may be performed by gel electrophoresis, particularly denaturing acrylamide or agarose gels. A convenient system uses denaturing polyacrylamide gels in combination with an automated DNA sequencer, see Hunkapillar *et al.* (1991) Science **254**:59-74. The automated sequencer is particularly useful with multiplex amplification or pooled products of separate PCR reactions. Capillary electrophoresis may also be used for fractionation. A review of capillary electrophoresis may be found in Landers, *et al.* (1993) BioTechniques **14**:98-111. The size of the amplification product is proportional to the number of repeats (n) that are present at the locus specified by the primers. The size will be polymorphic in the population, and is therefore an allelic marker for that locus.

A number of markers in the region of the ASTH1 locus have been identified, and are listed in Table 1 in the Experimental section (SEQ ID NOs:160-273). Of particular interest for diagnostic purposes is the marker D11S2008, in which individuals having alleles C or F at this locus, particularly in combination with the CAAT box polymorphism and other polymorphisms, are predisposed to develop bronchial hyperreactivity or asthma. The association of D11S2008 alleles is as follows:

Allele	Association with asthma	Number of TATC repeats relative to allele C (SEQ ID NO:15)
A	no	-2
B	no	-1
C	yes	equivalent
D	no	+1
E	no	+2
F	yes	+3
G	no	+4
H	no	+5

A DNA sequence of interest for diagnosis comprises the D11S2008 primer sequences shown in Table 1 (SEQ ID NO:242 and 243), flanking one or three repeats of SEQ ID NO:15.

Other microsatellite markers of interest for diagnostic purposes are CA39_2; 774F; 774J; 774O; L19PENTA1; 65P14TE1; AFM205YG5; D11S907; D11S4200; 774N; CA11-11; 774L; AFM283WH9; ASMI14 and D11S1900 (primer sequences are provided in Table 1, the repeats are provided in Table 1B).

Regulation of ASTH1 Expression

The *ASTH1* genes are useful for analysis of ASTH1 expression, *e.g.* in determining developmental and tissue specific patterns of expression, and for modulating expression *in vitro* and *in vivo.* The regulatory region of SEQ ID NO:1 may also be used to investigate analysis of *ASTH1* expression. Vectors useful for introduction of the gene include plasmids and viral vectors. Of particular interest are retroviral-based vectors, *e.g.* Moloney murine leukemia virus and modified human immunodeficiency virus; adenovirus vectors, *etc.* that are maintained transiently or stably in mammalian cells. A wide variety of vectors can be employed for transfection and/or integration of the gene into the genome of the cells. Alternatively, micro-injection may be employed, fusion, or the like for introduction of genes into a suitable host cell. See, for example, Dhawan *et al.* (1991) Science **254**:1509-1512 and Smith *et al.* (1990) Molecular and Cellular Biology 3268-3271.

Administration of vectors to the lungs is of particular interest. Frequently such methods utilize liposomal formulations, as described in Eastman *et al.* (1997) Hum Gene Ther **8**:765-773; Oudrhiri *et al.* (1997) P.N.A.S. **94**:1651-1656; McDonald et al. (1997) Hum Gene Ther **8**:411-422.

The expression vector will have a transcriptional initiation region oriented to produce functional mRNA. The native transcriptional initiation region, *e.g.* SEQ ID NO:14, or an exogenous transcriptional initiation region may be employed. The promoter may be introduced by recombinant methods *in vitro*, or as the result of homologous integration of the sequence into a chromosome. Many strong promoters are known in the art, including the β-actin promoter, SV40 early and late promoters, human cytomegalovirus promoter, retroviral LTRs, methallothionein responsive element (MRE), tetracycline-inducible promoter constructs, *etc.*

Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences. Transcription cassettes may be prepared comprising a transcription initiation region, the target gene or fragment thereof, and a transcriptional termination region. The transcription cassettes may be introduced into a variety of vectors, *e.g.* plasmid; retrovirus, *e.g.* lentivirus; adenovirus; and the like, where the vectors are able to transiently or stably be maintained in the cells, usually for a period of at least about one day, more usually for a period of at least about several days to several weeks.

Antisense molecules are used to down-regulate expression of *ASTH1* in cells. The anti-sense reagent may be antisense oligonucleotides (ODN), particularly synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such anti-sense molecules as RNA. The antisense sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. Antisense molecules inhibit gene expression through various mechanisms, *e.g.* by reducing the amount of mRNA available for translation, through activation of RNAse H, or steric hindrance. One or a combination of antisense molecules may be administered, where a combination may comprise multiple different sequences.

Antisense molecules may be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense oligonucleotides will generally be at least about 7, usually at least about 12, more usually at least about 20 nucleotides in length, and not more than about 500, usually not more than about 50, more usually not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, specificity, including absence of cross-reactivity, and the like. It has been found that short oligonucleotides, of from 7 to 8 bases in length, can be strong and selective inhibitors of gene expression (see Wagner *et al.* (1996) Nature Biotechnology **14**:840-844).

A specific region or regions of the endogenous sense strand mRNA sequence is chosen to be complemented by the antisense sequence. Selection of

a specific sequence for the oligonucleotide may use an empirical method, where several candidate sequences are assayed for inhibition of expression of the target gene in an *in vitro* or animal model. A combination of sequences may also be used, where several regions of the mRNA sequence are selected for antisense complementation.

Antisense oligonucleotides may be chemically synthesized by methods known in the art (see Wagner *et al.* (1993) *supra.* and Milligan *et al., supra.*) Preferred oligonucleotides are chemically modified from the native phosphodiester structure, in order to increase their intracellular stability and binding affinity. A number of such modifications have been described in the literature, which alter the chemistry of the backbone, sugars or heterocyclic bases.

Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoroamidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH2-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage. Sugar modifications are also used to enhance stability and affinity. The α-anomer of deoxyribose may be used, where the base is inverted with respect to the natural β-anomer. The 2'-OH of the ribose sugar may be altered to form 2'-O-methyl or 2'-O-allyl sugars, which provides resistance to degradation without comprising affinity. Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'-deoxycytidine and 5-bromo-2'-deoxycytidine for deoxycytidine. 5-propynyl-2'-deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

As an alternative to anti-sense inhibitors, catalytic nucleic acid compounds, *e.g.* ribozymes, anti-sense conjugates, *etc.* may be used to inhibit gene expression. Ribozymes may be synthesized *in vitro* and administered to the patient, or may be encoded on an expression vector, from which the ribozyme is synthesized in the

targeted cell (for example, see International patent application WO 9523225, and Beigelman et al. (1995) Nucl. Acids Res **23**:4434-42). Examples of oligonucleotides with catalytic activity are described in WO 9506764. Conjugates of anti-sense ODN with a metal complex, *e.g.* terpyridylCu(II), capable of mediating mRNA hydrolysis are described in Bashkin *et al.* (1995) Appl Biochem Biotechnol 54:43-56.

Therapeutic Use of ASTH1 Protein

A host may be treated with intact ASTH1 protein, or an active fragment thereof to modulate or reduce bronchial hypereactivity. Desirably, the peptides will not induce an immune response, particularly an antibody response. Xenogeneic analogs may be screened for their ability to provide a therapeutic effect without raising an immune response. The protein or peptides may also be administered to *in vitro* cell cultures.

Various methods for administration may be employed. The polypeptide formulation may be given orally, or may be injected intravascularly, subcutaneously, peritoneally, *etc.* Methods of administration by inhalation are well-known in the art. The dosage of the therapeutic formulation will vary widely, depending upon the nature of the disease, the frequency of administration, the manner of administration, the clearance of the agent from the host, and the like. The initial dose may be larger, followed by smaller maintenance doses. The dose may be administered as infrequently as weekly or biweekly, or fractionated into smaller doses and administered daily, semi-weekly, *etc.* to maintain an effective dosage level. In many cases, oral administration will require a higher dose than if administered intravenously. The amide bonds, as well as the amino and carboxy termini, may be modified for greater stability on oral administration.

The subject peptides may be prepared as formulations at a pharmacologically effective dose in pharmaceutically acceptable media, for example normal saline, PBS, *etc.* The additives may include bactericidal agents, stabilizers, buffers, or the like. In order to enhance the half-life of the subject peptide or subject peptide conjugates, the peptides may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or another conventional technique may be employed that provides for an extended lifetime of the peptides.

The peptides may be administered as a combination therapy with other pharmacologically active agents. The additional drugs may be administered separately or in conjunction with the peptide compositions, and may be included in the same formulation.

Models for Asthma

The subject nucleic acids can be used to generate genetically modified non-human animals or site specific gene modifications in cell lines. The term "transgenic" is intended to encompass genetically modified animals having a deletion or other knock-out of *ASTH1* gene activity, having an exogenous *ASTH1* gene that is stably transmitted in the host cells, or having an exogenous *ASTH1* promoter operably linked to a reporter gene. Transgenic animals may be made through homologous recombination, where the *ASTH1* locus is altered. Alternatively, a nucleic acid construct is randomly integrated into the genome. Vectors for stable integration include plasmids, retroviruses and other animal viruses, YACs, and the like. Of interest are transgenic mammals, *e.g.* cows, pigs, goats, horses, *etc.*, and particularly rodents, *e.g.* rats, mice, *etc.*

A "knock-out" animal is genetically manipulated to substantially reduce, or eliminate endogenous *ASTH1* function. Different approaches may be used to achieve the "knock-out". A chromosomal deletion of all or part of the native *ASTH1* homolog may be induced. Deletions of the non-coding regions, particularly the promoter region, 3' regulatory sequences, enhancers, or deletions of gene that activate expression of ASTH1 genes. A functional knock-out may also be achieved by the introduction of an anti-sense construct that blocks expression of the native *ASTH1* genes (for example, see Li and Cohen (1996) Cell 85:319-329).

Transgenic animals may be made having exogenous *ASTH1* genes. The exogenous gene is usually either from a different species than the animal host, or is otherwise altered in its coding or non-coding sequence. The introduced gene may be a wild-type gene, naturally occurring polymorphism, or a genetically manipulated sequence, for example those previously described with deletions, substitutions or insertions in the coding or non-coding regions. The introduced sequence may encode an ASTH1 polypeptide, or may utilize the *ASTH1* promoter operably linked to a reporter gene. Where the introduced gene is a coding sequence, it usually

operably linked to a promoter, which may be constitutive or inducible, and other regulatory sequences required for expression in the host animal.

Specific constructs of interest, but are not limited to, include anti-sense *ASTH1*, which will block ASTH1 expression, expression of dominant negative ASTH1 mutations, and over-expression of a ASTH1 gene. A detectable marker, such as *lac Z* may be introduced into the *ASTH1* locus, where upregulation of *ASTH1* expression will result in an easily detected change in phenotype. Constructs utilizing the *ASTH1* promoter region, *e.g.* SEQ ID NO:1; SEQ ID NO:14, in combination with a reporter gene or with the coding region of *ASTH1J* or *ASTH1I* are also of interest.

The modified cells or animals are useful in the study of *ASTH1* function and regulation. Animals may be used in functional studies, drug screening, *etc.*, *e.g.* to determine the effect of a candidate drug on asthma. A series of small deletions and/or substitutions may be made in the *ASTH1* gene to determine the role of different exons in DNA binding, transcriptional regulation, *etc.* By providing expression of ASTH1 protein in cells in which it is otherwise not normally produced, one can induce changes in cell behavior. These animals are also useful for exploring models of inheritance of asthma, *e.g.* dominant *v.* recessive; relative effects of different alleles and synergistic effects between *ASTH1I* and *ASTH1J* and other asthma genes elsewhere in the genome.

DNA constructs for homologous recombination will comprise at least a portion of the *ASTH1* gene with the desired genetic modification, and will include regions of homology to the target locus. DNA constructs for random integration need not include regions of homology to mediate recombination. Conveniently, markers for positive and negative selection are included. Methods for generating cells having targeted gene modifications through homologous recombination are known in the art. For various techniques for transfecting mammalian cells, see Keown *et al.* (1990) Methods in Enzymology **185:**527-537.

For embryonic stem (ES) cells, an ES cell line may be employed, or embryonic cells may be obtained freshly from a host, *e.g.* mouse, rat, guinea pig, *etc.* Such cells are grown on an appropriate fibroblast-feeder layer or grown in the presence of appropriate growth factors, such as leukemia inhibiting factor (LIF).

When ES cells have been transformed, they may be used to produce transgenic animals. After transformation, the cells are plated onto a feeder layer in an appropriate medium. Cells containing the construct may be detected by employing a selective medium. After sufficient time for colonies to grow, they are picked and analyzed for the occurrence of homologous recombination or integration of the construct. Those colonies that are positive may then be used for embryo manipulation and blastocyst injection. Blastocysts are obtained from 4 to 6 week old superovulated females. The ES cells are trypsinized, and the modified cells are injected into the blastocoel of the blastocyst. After injection, the blastocysts are returned to each uterine horn of pseudopregnant females. Females are then allowed to go to term and the resulting litters screened for mutant cells having the construct. By providing for a different phenotype of the blastocyst and the ES cells, chimeric progeny can be readily detected.

The chimeric animals are screened for the presence of the modified gene and males and females having the modification are mated to produce homozygous progeny. If the gene alterations cause lethality at some point in development, tissues or organs can be maintained as allogeneic or congenic grafts or transplants, or in *in vitro* culture.

Investigation of genetic function may utilize non-mammalian models, particularly using those organisms that are biologically and genetically well-characterized, such as *C. elegans*, *D. melanogaster* and *S. cerevisiae*. For example, transposon (Tc1) insertions in the nematode homolog of an *ASTH1* gene or promoter region may be made. The subject gene sequences may be used to knock-out or to complement defined genetic lesions in order to determine the physiological and biochemical pathways involved in *ASTH1* function. A number of human genes have been shown to complement mutations in lower eukaryotes.

Drug screening may be performed in combination with the subject animal models. Many mammalian genes have homologs in yeast and lower animals. The study of such homologs' physiological role and interactions with other proteins can facilitate understanding of biological function. In addition to model systems based on genetic complementation, yeast has been shown to be a powerful tool for studying protein-protein interactions through the two hybrid system described in

Chien *et al.* (1991) P.N.A.S. **88**:9578-9582. Two-hybrid system analysis is of particular interest for exploring transcriptional activation by *ASTH1* proteins.

Drug Screening Assays

By providing for the production of large amounts of ASTH1 protein, one can identify ligands or substrates that bind to, modulate or mimic the action of ASTH1. Areas of investigation are the development of asthma treatments. Drug screening identifies agents that provide a replacement or enhancement for ASTH1 function in affected cells. Conversely, agents that reverse or inhibit ASTH1 function may stimulate bronchial reactivity. Of particular interest are screening assays for agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled *in vitro* protein-protein binding assays, protein-DNA binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, and the like. The purified protein may also be used for determination of three-dimensional crystal structure, which can be used for modeling intermolecular interactions, transcriptional regulation, *etc.*

The term "agent" as used herein describes any molecule, *e.g.* protein or pharmaceutical, with the capability of altering or mimicking the physiological function of ASTH1. Generally a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, *i.e.* at zero concentration or below the level of detection.

Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including, but not limited to: peptides, saccharides, fatty acids,

steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, *etc.* to produce structural analogs.

Where the screening assay is a binding assay, one or more of the molecules may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, enzymes, specific binding molecules, particles, *e.g.* magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

A variety of other reagents may be included in the screening assay. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc that are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, *etc.* may be used. The mixture of components are added in any order that provides for the requisite binding. Incubations are performed at any suitable temperature, typically between 4 and 40°C. Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high-throughput screening. Typically between 0.1 and 1 hours will be sufficient.

Other assays of interest detect agents that mimic ASTH1 function. For example, candidate agents are added to a cell that lacks functional ASTH1, and screened for the ability to reproduce ASTH1 in a functional assay.

The compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host for treatment of asthma attributable to a defect in ASTH1function. The compounds may also be used to enhance ASTH1 function. The therapeutic agents may be administered in a variety of ways, orally, topically, parenterally *e.g.* subcutaneously, intraperitoneally, by viral infection, intravascularly, *etc.* Inhaled treatments are of particular interest. Depending upon the manner of introduction, the compounds may be formulated in a variety of ways. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt.%.

The pharmaceutical compositions can be prepared in various forms, such as granules, tablets, pills, suppositories, capsules, suspensions, salves, lotions and the like. Pharmaceutical grade organic or inorganic carriers and/or diluents suitable for oral and topical use can be used to make up compositions containing the therapeutically-active compounds. Diluents known to the art include aqueous media, vegetable and animal oils and fats. Stabilizing agents, wetting and emulsifying agents, salts for varying the osmotic pressure or buffers for securing an adequate pH value, and skin penetration enhancers can be used as auxiliary agents.

Pharmacogenetics

Pharmacogenetics is the linkage between an individual's genotype and that individual's ability to metabolize or react to a therapeutic agent. Differences in metabolism or target sensitivity can lead to severe toxicity or therapeutic failure by altering the relation between bioactive dose and blood concentration of the drug. In the past few years, numerous studies have established good relationships between polymorphisms in metabolic enzymes or drug targets, and both response and toxicity. These relationships can be used to individualize therapeutic dose administration.

Genotyping of polymorphic alleles is used to evaluate whether an individual will respond well to a particular therapeutic regimen. The polymorphic sequences

are also used in drug screening assays, to determine the dose and specificity of a candidate therapeutic agent. A candidate ASTH1 polymorphism is screened with a target therapy to determine whether there is an influence on the effectiveness in treating asthma. Drug screening assays are performed as described above. Typically two or more different sequence polymorphisms are tested for response to a therapy.

Drugs currently used to treat asthma include beta 2-agonists, glucocorticoids, theophylline, cromones, and anticholinergic agents. For acute, severe asthma, the inhaled beta 2-agonists are the most effective bronchodilators. Short-acting forms give rapid relief; long-acting agents provide sustained relief and help nocturnal asthma. First-line therapy for chronic asthma is inhaled glucocorticoids, the only currently available agents that reduce airway inflammation. Theophylline is a bronchodilator that is useful for severe and nocturnal asthma, but recent studies suggest that it may also have an immunomodulatory effect. Cromones work best for patients who have mild asthma: they have few adverse effects, but their activity is brief, so they must be given frequently. Cysteinil leukotrienes are important mediators of asthma, and inhibition of their effects may represent a potential breakthrough in the therapy of allergic rhinitis and asthma.

Where a particular sequence polymorphism correlates with differential drug effectiveness, diagnostic screening may be performed. Diagnostic methods have been described in detail in a preceding section. The presence of a particular polymorphism is detected, and used to develop an effective therapeutic strategy for the affected individual.

EXPERIMENTAL

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.* amounts, temperature, concentrations, *etc.*) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are

parts by weight, molecular weight is average molecular weight; temperature is in degrees centigrade; and pressure is at or near atmospheric.

MATERIALS AND METHODS

Asthma families for genetic mapping studies

Asthma phenotype measurements and blood samples were obtained from the inhabitants of Tristan da Cunha, an isolated island in the South Atlantic, and from asthma families in Toronto, Canada (see Zamel *et al.*, (1996) *supra.*) The 282 inhabitants of Tristan da Cunha form a single large extended family descended from 28 original founders. Settlement of Tristan da Cunha occurred beginning in 1817 with soldiers who remained behind when a British garrison was withdrawn from the island, followed by the survivors of several shipwrecks. In 1827 five women from St. Helena, one with children, emigrated to Tristan da Cunha and married island men. One of these women is said to have been asthmatic, and could be the origin of a genetic founder effect for asthma in this population. Inbreeding has resulted in kinship resemblances of at least first cousin levels for all individuals.

The Tristan da Cunha family pedigrees were ascertained through review of baptismal, marriage and medical records, as well as reliably accurate historical records of the early inhabitants (Zamel (1995) Can. Respir. J. **2**:18). The prevalence of asthma on Tristan da Cunha is high; 23% had a definitive diagnosis of asthma.

The Toronto cohort included 59 small families having at least one affected individual. These were ascertained based on the following criteria: (i) an affected proband; (ii) availability of at least one sibling of the proband, either affected or unaffected; (iii) at least one living parent from whom DNA could be obtained. A set of 156 "triad" families consisting of an affected proband and his or her parents were also collected. Signed consent forms were obtained from each individual prior to commencement of phenotyping and blood sample collection. The Toronto patients were mainly of mixed European ancestry.

Clinical characterization

A standardized questionnaire based on that of the American Thoracic Society (American Lung Association recommended respiratory diseases questionnaire for use with adults and children in epidemiology research. 1978. American Review of Respiratory Disease **118**(2):7-53) was used to record the presence of respiratory symptoms such as cough, sputum and wheezing; the presence of other chest disorders including recent upper respiratory tract infection, allergic history; asthmatic attacks including onset, offset, confirmation by a physician, prevalence, severity and precipitating factors; other illnesses and smoking history; and all medications used within the previous 3 months. A physician-confirmed asthmatic attack was the principal criterion for a diagnosis of asthma.

Skin atopy was determined by skin prick tests to common allergens: *A. fumigatus*, *Cladosporium, Alternaria*, egg, milk, wheat, tree, dog, grass, horse, house dust, cat, feathers, house dust mite *D. farinae*, and house dust mite *D. pteronyssinus*. Atopy testing of Toronto subjects omitted *D. pteronyssinus* and added cockroach and ragweed allergens. Saline and histamine controls were also performed (Bencard Laboratories, Mississauga, Ontario). Antihistamines were withdrawn for at least 48 hours prior to testing. Wheal diameters were corrected by subtraction of the saline control wheal diameter, and a corrected wheal size of >3 mm recorded 10 min after application was considered a positive response.

Airway responsiveness was assessed by a methacholine challenge test in those subjects with a baseline FEV1 (forced exhalation volume in one second) > 70% of predicted (Crapo *et al.* (1981) Am. Rev. Respir. Dis. **123**:659). Methacholine challenge response was determined using the tidal breathing method (Cockcroft *et al.* (1977) Clin. Allergy **7**:235). Doubling doses of methacholine from 0.03 to 16 mg/ml were administered using a Wright nebulizer at 4-min intervals to measure the provocative concentration of methacholine producing a 20% fall in FEV1 (PC20). If FEV1 was <70% of predicted, a bronchodilator response to 400 mg salbutamol aerosol was used to determine airway responsiveness. Both methacholine challenges and bronchodilator responses were measured using a computerized bronchial challenge system (S&M Instrument Co. Inc., Doyleston, PA)

consisting of a software package and interface board installed in a Toshiba T1850C laptop computer and connected to a flow sensor (RS232FS). The power source for instruments used on Tristan da Cunha has been described (Zamel *et al.* (1996) *supra.*) Increased airway responsiveness was defined as a PC20 < 4.0 mg/ml or a > 15% improvement in FEV1 15 min postbronchodilator. Participants were asked to withhold bronchodilators at least 8 h before testing; inhaled or systemic steroids were maintained at the usual dosage. Subjects with a history of an upper respiratory tract infection within a month of testing were rechallenged at a later date.

Genotyping

PCR primer pairs were synthesized using Applied Biosystems 394 automated oligo synthesizer. The forward primer of each pair was labeled with either FAM, HEX, or TET phosphoramidites (Applied Biosystems). No oligo purification step was performed.

Genomic DNA was extracted from whole blood. PCR was performed using PTC100 thermocyclers (MJ Research). Reactions contained 10 mM Tris-HCl, pH 8.3; 1.5-3.0 mM $MgCl_2$; 50 mM KCl; 0.01% gelatin; 250 μM each dGTP, dATP, dTTP, dCTP; 20 μM each PCR primer; 20 ng genomic DNA; and 0.75 U Taq Polymerase (Perkin Elmer Cetus) in a final volume of 20 μl. Reactions were performed in 96 well polypropylene microtiter plates (Robbins Scientific) with an initial 94°C, 3 min. denaturation followed by 35 cycles of 30 sec. at 94°C, 30 sec. at the annealing temp., and 30 sec. at 72°C, with a final 2 min. extension at 72°C following the last cycle. Dye label, annealing temperature, and final magnesium concentration were specific to the individual marker.

Dye label intensity and quantity of PCR product (as assessed on agarose gels) were used to determine the amount to be pooled for each marker locus. The pooled products were precipitated and the product pellets mixed with 0.4 μl Genescan 500 Tamra size standard, 2 μl formamide, and 1 μl ABI loading dye. Plates of PCR product pools were heated to 80°C for 5 minutes and immediately placed on ice prior to gel loading.

PCR products were electrophoresed on denaturing 6% polyacrylamide gels at a constant 1000 volts using ABI 373a instruments. Peak detection, sizing, and stutter band filtering were achieved using Genescan 1.2 and Genotyper 1.1 software (Applied Biosystems). Genotype data were subsequently submitted to quality control and consistency checks (Hall *et al.* (1996) Genome Res. **6**:781).

Genotyping of 'saturation' markers in the ASTH1 region was done by the method described above with several exceptions. In most cases, the unlabeled primer of each pair was modified with the sequence GTTTCTT at the 5' end (Smith *et al.* 1995 Genome Res. **5**:312). Amplitaq Gold (Perkin Elmer Cetus) and buffer D (2.5 mM $MgCl_2$, 33.5 mM Tris-HCl pH 8.0, 8.3 mM $(NH_4)_2SO_4$, 25 mM KCl, 85 µg/ml BSA) were used in the PCR. A 'touchdown' amplification profile was employed in which the annealing temperature began at 66°C and decreased one degree per cycle to a final 20 cycles at 56°C. Products were run on 4.25% polyacrylamide gels using ABI 377 instruments. The data was processed with Genescan 2.1 and Genotyper 1.1 software.

The Genome Scan

A genome scan was performed in the population of Tristan da Cunha using 274 polymorphic microsatellite markers chosen from among those developed at Oxford (Reed *et al.* (1994) Nature Genetics **7**:390), Genethon (Dib *et al.* (1996) Nature **380**:152) and the Cooperative Human Linkage Center (CHLC, Murray *et al.* (1994) Science **265**:2049). Markers with heterozygosity values of 0.75 or greater were selected to cover all the human chromosomes, as well as for ease of genotyping and size of PCR product for multiplexing of markers on gels. Fifteen multiplexed sets were used to provide a ladder of PCR products in each of three dyes when separated by size. Published distances were used initially to estimate map resolution. More accurate genetic distances were calculated using the study population as the data was generated. The 274 markers gave an average 14 cM interval for the genome scan.

Linkage analysis

Parametric linkage analyses of marker data were conducted using the methods of Haseman and Elston (1972) Behav. Genet. **2**:3, and FASTLINK (Schaffer *et al.* (1996) Hum. Hered. **46**:226), assuming a dominant mode of transmission with incomplete penetrance. Linkage to three primary phenotypes including asthma diagnosis (history), airway responsiveness (PC20 < 4 mg/ml for methacholine challenge) and atopy (one or more skin-prick test which yielded a wheal diameter > 3 mm) and combinations of these, were tested.

Small scale yeast artificial chromosome (YAC) DNA preparation

Small scale isolation of YAC DNA for STS mapping was done by a procedure which uses glass beads and physical shearing to damage the yeast cell wall (Scherer and Tsui (1991) Cloning and analysis of large DNA molecules, In Advanced Techniques in Chromosome Research. (K.W. Adolph, ed.) pp. 33-72. Marcel Dekker, Inc. New York, Basel, Hong Kong.)

YAC block prep and pulsed field gel electrophoresis (PFGE)

A 50 ml culture of each YAC was grown in 2 x AHC at 30°C. The cells were pelleted by centrifugation and washed twice in sterile water. After resuspension of the cells in 4 ml of SCEM (1 M sorbitol, 0.1 M sodium citrate (pH 5.8), 10 mM EDTA, 30 mM β-mercaptoethanol), 5 ml of 1.2% low melting temperature agarose in SCEM was added, mixed, pipetted into 100 ml plug molds and allowed to solidify. Plugs were incubated overnight in 50 ml of SCEM containing 30 U/ml lyticase (Sigma). Plugs were rinsed 3 times in TE (10 mM Tris pH 8.0, 1 mM EDTA) and incubated twice for 12 hours each at 50°C in lysis solution (0.5 M EDTA, pH 8.0; 1% w/v sodium lauryl sarcosine; 0.5 mg/ml proteinase K). They were washed 5 times with TE and stored in 0.5 M EDTA (pH 8.0) at 4°C.

YACs and yeast chromosomes were separated on pulsed field gels using a CHEF Mapper (BIO-RAD) and according to methods supplied by the manufacturer, then transferred to nitrocellulose. YACs which comigrated with yeast chromosomes were visualized by hybridization of the blot with radiolabelled YAC vector sequences (Scherer and Tsui (1991) *supra*.)

Hybridization of YAC DNA to bacterial artificial chromosome (BAC) and cosmid grids

Size-purified YAC DNA was prepared by pulsed field gel electrophoresis on a low melting temperature Seaplaque GTG agarose (FMC) gel, purified by GeneClean (BIO101) and radiolabeled for 30 mins with ^{32}P-dCTP using the Prime-It II kit (Stratagene). 50 μl of water was added and unincorporated nucleotide was removed by Quick Spin Column (Boehringer Mannheim). 23 μl of 11.2 mg/ml human placental DNA (Sigma) and 36 μl of 0.5 M Na_2HPO_4, pH 6.0 were added to the approximately 150 μl of eluant. The probe was boiled for 5 mins and incubated at 65°C for exactly 3 hours, then added to the prehybridized gridded BAC (Shizuya *et al.* (1992) Proc. Natl. Acad. Sci. **89**:8794; purchased from Research Genetics) or chromosome 11 cosmid [Resource Center/ Primary Database of the German Human Genome Project, Berlin; Lehrach *et al.* (1990), In Davies, K.E. and Tilghman, S.M. (eds.), Genome Analysis Volume 1: Genetic and Physical Mapping. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, pp. 39-81] filters in dextran sulfate hybridization mix (10% dextran sulfate, 1% SDS, 1 M NaCl). Hybridizations were at 65°C for 12 - 48 hours, followed by 2 washes at room temperature in 2x SSC for 10 mins each, and 3 washes at 65°C in 0.2X SSC, 0.2% SDS for 20 mins each.

Metaphase fluorescence in situ hybridization (FISH) and direct visual in situ hybridisation (DIRVISH)

Metaphase FISH was carried out by standard methods (Heng and Tsui (1994) FISH detection on DAPI banded chromosomes. In Methods of Molecular Biology: In Situ Hybridisation Protocols (K.H.A. Choo, ed.) pp. 35-49. Human Press, Clifton, N.J.). High resolution FISH, or DIRVISH, was used to map the relative positions of two or more clones on genomic DNA. The protocol used was as described by Parra and Windle (1993) Nature Genet. **5**:17. Briefly, slides containing stretched DNA were prepared by adding 2 μl of a suspension of normal human lymphoblast cells at one end of a glass slide and allowing to dry. 8 μl lysis buffer (0.5% SDS, 50 mM EDTA, 200 mM Tris-HCL, pH 7.4) was added and the

slide incubated at room temperature for 5 minutes. The slide was tilted so that the DNA ran down the slide, then dried. The DNA was fixed by adding 400 μl 3:1 methanol/acetic acid. Probes were labeled either with biotin or with digoxygenin by standard nick translation (Rigby *et al.* (1977) J. Mol. Biol. **113**:237). Hybridization and detections were carried out using standard fluorescence *in situ* hybridization techniques (Heng and Tsui (1994) *supra.*). Results were visualised using a Mikrophot SA microscope (Nikon) equipped with a CCD camera (Photometrics). Images were recorded using Smartcapture software (Vysis).

Gap filling

Clones flanking gaps in the map were end cloned by digestion with enzymes that do not cut the respective vector sequences (NsiI for BAC clones and XbaI for PAC clones), followed by religation and transformation into competent DH5α. Clones which produced two end fragments and plasmid vector upon digestion with NotI and NsiI or XbaI were sequenced. Gaps in the tiling path were filled by screening a gridded BAC library with the end clone probes or by screening DNA pools of a human genomic PAC library (Ioannou *et al.* (1994) Nature Genetics **6**:84; licensed from Health Research, Inc.) by PCR using primers designed from end clone sequences.

Direct cDNA selection

Direct cDNA selection (Lovett *et al.,* (1991) Proc. Natl. Acad. Sci. 88:9628) was carried out using cDNA derived from both adult whole lung tissue and fetal whole lung tissue (Clontech). 5 μg of Poly(A)+ RNA was converted to double stranded cDNA using the Superscript Choice System for cDNA synthesis and the supplied protocol (Gibco BRL). First strand priming was achieved by both oligo(dT) and random hexamers. The resulting cDNA was split into 2 equal aliquots and digested with either MboI or TaqI prior to the addition of specific linker primers. Linker primers for MboI-digested DNA were as described by Morgan *et al.* (1992) Nucleic Acid Res. **20**:5173. Linker primers for TaqI-digested DNA were a modification of these:

(SEQ ID NO:336) Taq1a: 5'-CGAGAATTCACTCGAGCATCAGG;
(SEQ ID NO:337) Taq1b: 5'-CCTGATGCTCGAGTGAATTCT. The modified cDNA was ethanol precipitated and resuspended in 200 µl of H_2O. 1 µl of cDNA was amplified with the linker primer Mbo1b in a 100 µl PCR reaction. The resulting cDNA products, approximately 1 µg, were blocked with 1 µg of COT1 DNA (Gibco BRL) for 4 hours at 60°C in 120 mM $NaPO_4$ buffer, pH 7.0.

Approximately 1 µg of the appropriate genomic clones was biotinylated using the BioNick Labeling System (Gibco BRL). Unincorporated biotin was removed by spin column chromatography. Approximately 100 ng of biotinylated genomic DNA was denatured and allowed to hybridize to 1 µg of blocked cDNA in a total volume of 20 µl in 120 mM $NaPO_4$ for 60 hours at 60°C under mineral oil. After hybridization, the biotinylated DNA was captured on streptavidin-coated magnetic beads (Dynal) in 100 µl of binding buffer (1 M NaCl, 10 mM Tris, pH 7.4, 1 mM EDTA) for 20 minutes at room temperature with constant rotation. Two 15 minute washes at room temperature with 500 µl of 1X SSC/0.1% SDS were followed by four washes for 20 minutes at 65°C with 500 ul of 0.1X SSC/0.1% SDS with constant rotation. After each wash, the beads were collected on the side of the tube using magnet separation and the supernatant was removed with a pipette. Following the last wash, the beads were briefly rinsed once with wash solution prior to eluting the bound cDNA with 50 µl of 0.1 M NaOH for 10 minutes at room temperature. The supernatant was removed and neutralized with 50 µl 1 M Tris pH 7.4. The primary selected cDNA was desalted using a Sephadex G-50 column (Boehringer Mannheim). PCR was performed on 1, 2, 5, and 10 µl of eluate with Mbo1b primers. Amplified products were analyzed on a 1.4% agarose gel. The reaction with the cleanest bands and least background was scaled up to produce approximately 1 µg of primary selected cDNA. This amplified primary selected cDNA was blocked with 1 µg of COT1 at 60°C for 1 hour followed by a second round of hybridization to 100 ng of the appropriate genomic DNA under the same conditions as the first round of selection. Washing of the bound cDNA, elution, and PCR of the selected cDNA was identical to the first round. 1 µl of PCR amplified secondary selected cDNA was cloned using the TA cloning system according to the

manufacturers protocol (Invitrogen). Colonies were picked into 96-well microtiter plates and grown overnight prior to sequencing.

Exon Trapping

Exon trapping was performed by the method of Buckler *et al.* (1991, Proc. Natl. Acad. Sci. USA **88**:4005) with modifications described in Church *et al.*, (1994) Nature Genetics **6**:98. Each BAC clone of the minimal set of clones required to the cover the ASTH1 region (*i.e.* the tiling path) was subject to exon trapping separately. Briefly, restriction fragments (PstI or BamHI/BglII) of each cosmid were shotgun subcloned into PstI- or BamHI-digested and phosphatase-treated pSPL3B which had been modified as in Burns *et al.* (1995) Gene **161**:183 (GIBCO BRL). Ligations were electroporated into ElectroMax HB101 cells (Gibco BRL) and plated on 20 cm diameter LB ampicillin plates. DNA was prepared from plates with > 2000 colonies by collection of the bacteria in LB ampicillin liquid and plasmid DNA purification by a standard alkaline lysis protocol (Sambrook *et al.* (1989) *supra.*) 5 μg of DNA from each plasmid pool preparation were electroporated into Cos 7 cells (ATCC) and RNA harvested using TRIZOL (Gibco BRL) after 48 hours of growth. RT-PCR products were digested with BstXI prior to a second PCR amplification. Products were cloned into pAMP10 (Gibco BRL) and transformed into DH5 cells (Gibco BRL). 96 colonies per BAC were picked and analyzed for insert size by PCR.

Northern blot hybridisation

Northern hybridisation was performed using Multiple Tissue Northern (MTN) blots (Clontech). DNA probes were radioactively labeled by random priming [Feinberg and Vogelstein (1984) Anal. Biochem. **137**:266] using the Prime-It II kit (Stratagene). Hybridizations were performed in ExpressHyb hybridisation solution (Clontech) according to the manufacturer's recommendations. Filters were exposed to autoradiographic film overnight or for 3 days.

cDNA library screening

Phage cDNA libraries were plated and screened with radiolabeled probes (exon trapping or cDNA selection products amplified by PCR from plasmids containing these sequences) by standard methods (Sambrook *et al.* (1989) *supra.*)

Rapid amplification of cDNA ends (RACE)

RACE libraries were constructed using polyA+ RNA and the Marathon cDNA amplification kit (Clontech). Nested RACE primer sets were designed for each cDNA or potential gene fragment (trapped exon, predicted exon, conserved fragment, *etc*). The RACE libraries were tested by PCR using one primer pair for each potential gene fragment; the two strongly positive libraries were chosen for RACE experiments.

Genomic sequencing

DNA from cosmid, PAC, and BAC clones was prepared using Qiagen DNA prep kits and further purified by CsCl gradient. DNA was sonicated and DNA fragments were repaired using nuclease BAL-31 and T4 DNA polymerase. DNA fragments of 0.8-2.2 kb were size-fractionated by agarose gel electrophoresis and ligated into pUC9 vector. Inserts of the plasmid clones were amplified by PCR and sequenced using standard ABI dye-primer chemistry.

ABI sample file data was reanalyzed using Phred (Phil Green, University of Washington) for base calling and quality analysis. Sequence assembly of reanalyzed sequence data was accomplished using Phrap (Phil Green, University of Washington). Physical gaps between assembled contigs and unjoined but overlapping contigs were identified by inspection of the assembled data using GFP (licensed from Baylor College of Medicine) and Consed (Phil Green, University of Washington). Material for sequence data generation across gaps was obtained by PCR amplification. Low coverage regions were resequenced using dye-primer and dye-terminator chemistries (ABI). Final base-perfect editing (to > 99% accuracy) was accomplished using Consed.

Single stranded conformational polymorphism (SSCP) analysis -

PCR primers flanking each exon of the ASTH1I and ASTH1J genes, or more than one primer pair for large exons, were designed from genomic sequence generated using Primer (publicly available from the Whitehead Institute for Biomedical Research) or Oligo 4.0 (licensed from National Biosciences). Radioactive SSCP was performed by the method of Orita *et al.* (1989, Proc. Natl. Acad. Sci. **86**:2766). Briefly, radioactively labeled PCR products between 150 and 300 bp and spanning exons of the ASTH1I and ASTH1J genes were generated from a set of asthma patient and control genomic template DNAs, by incorporating α-^{32}P dCTP in the PCR. PCR reactions (20 μl) included 1x reaction buffer, 100 μM dNTPs, 1 μM each forward and reverse primer, and 1 unit Taq DNA polymerase (Perkin-Elmer) and 1 μCi α-^{32}P dCTP. A brief denaturation at 94°C was followed by 30-32 cycles of: 94°C for 30 sec, 30 sec at the annealling temperature, and 72°C for 30 sec; followed by 5 mins at 72°. Radiolabeled PCR products were diluted 1:20 in water, mixed with an equal volume of denaturing loading dye (95% formamide, 0.25% bromophenol blue), and denatured for 10 minutes at 80°C immediately prior to electrophoresis. 0.5x MDE (FMC) gels with and without 8% glycerol in 1x TBE were run at 8-12 Watts for 16-20 hours at room temperature. Dried gels were exposed to autoradiographic film (Kodak XAR) for 1-2 days at -80°C. PCR products from individuals carrying SSCP variants were subcloned into the PCR2.1 or pZeroBlunt plasmid vector (Invitrogen). Inserts of the plasmid clones were amplified by PCR and sequenced using standard ABI dye-primer chemistry to determine the nature of the sequence variant responsible for the conformational changes detected by SSCP.

Fluorescent SSCP was carried out according to the recommended ABI protocol (ABI User Bulletin entitled 'Multi Color Fluorescent SSCP'). Unlabeled PCR primers were used to amplify genomic DNA segments containing different exons of the ASTH1I or ASTH1J genes, in patient or control DNA. Nested fluorescently labeled (TET, FAM or HEX) primers were then used to amplify smaller products, 150 to 300 bp containing the exon or region of interest. Amplification was done using a `touchdown' PCR protocol, in which the annealing temperature

decreased from 57°C to 42°C, and Amplitaq Gold polymerase (Perkin Elmer, Cetus). In most cases the fluorescently labeled primers were identical in sequence to those used for conventional radioactive SSCP. The fluorescent PCR products were diluted and mixed with denaturing agents, GeneScan size standard (Genescan 500 labelled with Tamra) and Blue dextran dye. Samples were heated at 90°C and quick chilled on ice prior to loading on 6.5% standard or 0.5 X MDE (manufacturer) polyacrylamide gels containing 2.5% glycerol and run using externally temperature controlled modified ABI 377 instruments. Gels were run at 1240V and 20°C for 7-9 hrs and analyzed using GeneScan software (ABI).

Comparative (heterozygote detection) sequencing

Unlabeled PCR primers were used to amplify genomic DNA segments containing different exons of the ASTH1I or ASTH1J genes, from patient or control DNAs. A set of nested PCR primers was then used to reamplify the fragment. Unincorporated primers were removed from the PCR product by Centricon-100 column (Amicon), or by Centricon-30 column for products less than 130 bp. The nested primers and dye terminator sequencing chemistry (ABI PRISM dye terminator cycle sequencing ready reaction kit) were then used to cycle sequence the exon and flanking region. Volumes were scaled down to 5 μl and 10% DMSO added to increase peak height uniformity. Sequences were compared between samples and heterozygous positions detected by visual inspection of chromatograms and using Sequence Navigator (licensed from ABI).

For some exons, PCR products were also compared by subcloning and sequencing, and comparison of sequences for ten or more clones.

<u>RESULTS</u>

Genome scanning and linkage analysis

A genome scan was performed using polymorphic microsatellite markers from throughout the human genome, and DNA isolated from blood samples drawn from the inhabitants of Tristan da Cunha. Linkage analysis, an established statistical method used to map the locations of genes and markers relative to other markers, was applied to verify the marker orders and relative distances between

markers on all human chromosomes, in the Tristan da Cunha population. Linkage analysis can detect cosegregation of a marker with disease, and was used as a means to detect genes influencing the development of asthma in this population. The most highly significant linkage in the genome scan (p = 0.0001 for history of asthma and p = 0.0009 for methacholine challenge) was obtained at D11S907, a marker on the short arm of chromosome 11. This significant linkage result indicated that a gene influencing predisposition to asthma in the Tristan da Cunha population was located near D11S907.

Replication of this finding was obtained in a collection of asthma families from Toronto, in which D11S907 and several nearby markers were tested for linkage. The significant linkage seen (p = 0.001 for history of asthma and p = 0.05 for methacholine challenge) supported the mapping of an asthma gene near D11S907 and indicated that the gene was likely to be relevant in the more diverse outbred Toronto group as well as in the inbred population of Tristan da Cunha.

The approximate genetic location of the ASTH1 gene in the Tristan da Cunha population was confirmed by genotyping and analyzing data from several markers near D11S907, spaced at intervals no greater than 5 cM across a possible linked region of about 30 cM. Sib-pair and affected pedigree member linkage analyses of these markers yielded confirmatory evidence for linkage and refined the genetic interval.

Physical mapping at ASTH1: YAC contig construction

Yeast artificial chromosome (YAC) clones were derived from the CEPH megaYAC library (Cohen *et al.* 1993 Nature **366:**698). Individual YAC addresses were obtained from a public physical map of CEPH megaYAC STS (sequence tagged site; Olson *et al.* (1989) Science **245**:1434) mapping data maintained by the Whitehead Institute and accessible through the world wide web (Cohen *et al.* 1993. *supra.*; http://www-genome.wi.mit.edu/cgi-bin/contig/phys_map). YAC clones spanning or overlapping other YACs containing D11S907 were chosen for map construction; STSs mapping to these YACs were used for map and clone verification. Some YACs annotated in the public database as being chimeric were excluded from the analyses. Multiple colonies of each YAC, obtained from a freshly

streaked plate inoculated from the CEPH megaYAC library masterplate, were scored using STS markers from the ASTH1 region. These markers included polymorphic microsatellite repeats, expressed sequence tags (ESTs) and STSs. Comparison of STS mapping data for each clone with the public map allowed choice of the individual clone which retained the greatest number of ASTH1 region STSs, and was therefore least likely to be deleted. YAC addresses for which clones differed in STS content were interpreted to be prone to deletion; those for which a subset of clones contained no ASTH1 region STSs were presumed to be contaminated with yeast cells containing a YAC from another region of the genome. Chimerism of the chosen clones was assessed by metaphase fluorescent *in situ* hybridization (FISH). Their sizes were determined by pulsed field gel electrophoresis (PFGE), Southern blotting and hybridization with a YAC vector probe. The PFGE analyses also showed that no YAC clone chosen contained more than one yeast artificial chromosome.

An STS map based on assuming the least number of deletions in the YAC clones was generated. The STS marker order was in agreement with that of the Whitehead map. The STS retention pattern of individual YACs, however, was slightly different from that of the public data. In general, the chosen clones were positive for a greater number ASTH1 region markers, showing that the data set was likely to have fewer false negatives than the public map. Non-chimeric YAC clones spanning the region of greatest interest were chosen for use as hybridization probes for the identification of smaller BAC, PAC, P1 or cosmid clones from the region.

Conversion to a plasmid-based clone map

The YAC map at *ASTH1* provided continuous coverage of a 4 Mb region, the central 1 Mb of which was of greatest interest. YAC clones comprising a minimal tiling path of this region were chosen, and the size purified artificial chromosomes were used as hybridization probes to identify BAC and cosmid clones. Gridded filters of a 3x human genomic BAC library and of a human chromosome 11-specific cosmid library were hybridized with radiolabeled purified YAC. Clones corresponding to the grid coordinates of the positives were streaked to colony

purity, and filters gridded with four clones of each BAC or cosmid. These secondary filters were hybridized with size-purified YAC DNAs. A proportion of both the BACs and cosmids were found to be non-clonal by these analyses. A positively hybridizing clone of each was chosen for further analysis.

The BAC and cosmid clones were STS mapped to establish overlaps between the clones. The BACs were further localized by DIRVISH. BACs which did not contain an STS marker were mapped in pairwise fashion by simultaneous two-color DIRVISH with another BAC. The map produced had three gaps which were subsequently filled by end cloning and hybridization of the end clones to a human genomic PAC library. Genetic refinement of the *ASTH1* region had occurred concurrently with mapping, rendering it unnecessary to extend the BAC-contigged region. Mapping data was recorded in ACeDB (Eeckman and Durbin (1995) Methods Cell Biol. **48**:583).

Genomic sequencing and gene prediction

A minimal tiling path of BAC and cosmid clones was chosen for genomic sequencing. Over 1 Mb of genomic sequence was generated at *ASTH1*. On average, sequencing was done to 12x coverage (12 times redundancy in sequences). Marker order was verified relative to the STS map.

BLAST searches (Altschul *et al.* (1990) *supra.*) were performed to identify sequences in public databases that were related to those in the *ASTH1* region. Sequence-based gene prediction was done with the GRAIL [Roberts (1991) Science **254**:805] and Geneparser [Snyder and Stormo (1993) Nucleic Acids Res. **21**: 607] programs. Genomic sequence and feature data was stored in ACeBD.

Development of new microsatellite markers for genetic refinement of the ASTH1 region

Additional informative polymorphic markers were important for the genetic refinement of the *ASTH1* region. 'Saturation' cloning of every microsatellite in the 1 Mb region surrounding D11S907 was performed. Plasmid libraries were constructed from PFGE purified DNA from each YAC, prescreened with a primer from each known microsatellite marker, then screened with radiolabeled (CA)15 or

a pool of trinucleotide and tetranucleotide repeat oligonucleotides. The plasmid inserts were sequenced, the set of sequences compared with those of the known microsatellite markers in the region, using Power assembler (ABI) or Sequencher (Alsbyte). Primer pairs flanking each novel microsatellite repeat were designed, and the heterozygosity of each new marker was tested by Batched Analysis of Genotypes (BAGs; LeDuc *et al.*, 1995, PCR Methods and Applications **4**:331). Additional microsatellites were found by analysis of the genomic sequence in AceDB. Table 1 lists all the microsatellite markers used for genotyping in the ASTH1 region and their repeat type, source and primers. Table 1B lists some repeat sequences.

TABLE 1

Polymorphic microsatellite markers in the *ASTH1* region

SEQ ID	MARKER	PRIMER 1
160.	110O5GT1	CTGCTGTGGACGAATAGG
161.		TCAATATAATCTTGCTTAACTTGG
162.	139C7GT1	GACCTGTTTGGGTTGATTTCAG
163.		GTTTCTTACAGTGTCTTGCTATCACATCACC
164.	171L24AT1	GAGGACTGGCAGTACCAAGTAAAC
165.		GTTTCTTTGGTTCATTCTAAGATGGCTGG
166.	253E6GT1	GCTGAGGCAGGAGAAAAGACAAG
167.		GTTTCTTCATGCAAAGGTCAGGAGGTAGG
168.	253E6TE1	GTTGCTTCCAGACGAGGTACATG
169.		GTTTCTTCAATGGCTCCACAAACATCTCTG
170.	253E6TR1	AGGTTTAGGGGACAGGGTTTGG
171.		GTTTCTTTCCTGGCTAACACGGTGAAATC
172.	65P14	GTTTCTTATTGCCTCCTCCCAAAATTC
173.		AGAGGCCACTGGAAGACGAA
174.	65P14GT1	AACTGGAGTCAGGCAAAACGTG
175.		GTTTCTTTGGCTGGTAAGGAAAGAAACCAC
176.	65P14TE1	GGCTAGGTTCATAAACTCTGTGCTG
177.		GTTTCTTGATTGTTTGAGATCCTTGACCCAG
178.	65P14TE2	GCCGAAATCACAACACTGCATC
179.		GTTTCTTGATTCTGCTCTTACTCTTGCCCC

180.	65P14TR1	GTAATAGAACCAAAGGGCTGAGAC
181.		GTTTCTTCGGAGTCAGACCTTACATTGTTGAG
182.	774F	ATCTCCCTGCTACCCACCTT
183.		GTTTCTTGTTTTCAGTGAGTTTCTGTTGGG
184.	774J	GTGTGCCAAACAACATTTGC
185.		GTTTCTTCAAGCCATCAAGCTAGAGTGG
186.	774L	GGGCTTTTAAACCCTTATTTAACC
187.		GTTTCTTAGGTGATCTCAGAGCCACTCA
188.	774N	AGGGCAGGTGGGAACTTACT
189.		GTTTCTTTGGAGTCAGTTGAGCTTTCTACC
190.	774O	TGAACTTGCCTACCTCCCAG
191.		GTTTCTTAGCATATATCCTTACACAAGCACA
192.	774T	CATGGTTCCAAAGGCAAGTT
193.		GTTTCTTTTGAGGCTGAATGAGCTGTG
194.	86J5AT2	ACAGGTGGGAAGACTGAATGTC
195.		GTTTCTTGCAGTACACATCACATGACCTTG
196.	86J5CA1	GAAATAGGCGGAAACTGGTTC
197.		GTTTCTTCGTTGTGGTTGTTCAGAAAGG
198.	86J5GT1	GGTCAAGTGTTCAGAACGCATC
199.		GTTTCTTGCAGGGATTATGCTAGGTCTGTAG
200.	86J5GT2	AGCACTTCTGAGGAAGGGACAC
201.		GTTTCTTAGGGCAGGCAGACATACAAAC
202.	86J5TE1	GCCAATGTGTTCCTAGAGCGAC
203.		GTTTCTTTTAAAGGGGGTAGGGTGTCACC
204.	8E.PENTA1	GGAAGGGAAAAGGACAAGGTTTTG
205.		GTTTCTTAGCAAGAGCACTGGTGTAGGAGTC
206.	8EP04D05	GCTTTTCAAGCACTTGTCTC
207.		TGGGATTGTGACTTACCATG
208.	8O16GT1	ACTTGGTGTCTTATAGAAAGGTG
209.		GTTTCTTAGCTGTGTTTGCTGCATC
210.	8O16GT2	AGATGTGTGATGAGATGCAG
211.		GTTTCTTCAAATAGTGCAACAAACCC
212.	AFM198YB10(G)	TGTCATTCTGAAAGTGCTTCC

213.		GTTTCTTCTGTAACTAACGATCTGTAGTGGTG
214.	AFM205YG5(G)	TATCAAGGTAATATAGTAGCCACGG
215.		AGGTCTTTCATGCAGAGTGG
216.	AFM206XB2(G)	ATTGCCAAAACTTGGAAGC
217.		AGGTGACATATCAAGACCCTG
218.	AFM283WH9(G)	TTGTCAACGAAGCCCAC
219.		GTTTCTTGCAAGATTGTGTGTATGGATG
220.	AFM324YH5(G)	GCTCTCTATGTGTTTGGGTG
221.		AAGAGTACGCTAGTGGATGG
222.	AFMA154ZD1(G)	TCCATTAGACCCAGAAAGG
223.		GTTTCTTCACCAGGCTGAGATGTTACT
224.	ASMI14	AATCGTTCCTTATCAGGTAATTTGG
225.		GTTTCTTCAAAGAAAGCAATTCCATCATAACA
226.	ASMI14T	GCATTTGTTGAAGCAAGCGG
227.		CTTTGTTCCTTGGCTGATGG
228.	CA11_11	AATAGTACCAGACACACGTG
229.		CAATGGTTCACAGCCCTTTT
230.	CA39_2	AGCCTGGGAGACAGAGTGAG
231.		GTTTCTTGCACTTTTTGGGGAAGGTG
232.	CD59(L)	GTTCCTCCCTTCCCTCTCC
233.		GTTTCTTTCAGGGACTGGATTGTAG
234.	D11S1301(U)	GTGTTCTTTATGTGTAGTTC
235.		GTTTCTTGGCAACAGAGTGAGACTCA
236.	D11S1751(G)	GTGACATCCAGTGTTGGGAG
237.		GTTTCTTCCTAAGCAAGCAAGCAATCA
238.	D11S1776(G)	AAAGGCAATTGGTGGACA
239.		GTTTCTTTTCAATCCTTGATGCAAAGT
240.	D11S1900(U)	GGTGACAGAGCAAGATTTCG
241.		GTTTCTTGTAGAGTTGAGGGAGCAGC
242.	D11S2008/D11S1392 (C)	CATCCATCTCATCCCATCAT
243.		GTTTCTTTTCACCCTACTGCCAACTTC
244.	D11S2014(C)	CCGCCATTTTAGAGAGCATA

245.		GTTTCTTTTCTGGGACAATTGGTAGGA
246.	D11S4200(G)	TTTGTGTTATTATTTCAGGTGC
247.		GTTTCTTGTTTTTTGTTTCA GTTTAGGAAC
248.	D11S907(G)	CATACCCAAATCGTTCTCTTCCTC
249.		GTTTCTTGGAAAAGCAAAG GCATCGTAGAG
250.	D11S935(G)	TACTAACCAAAAGAGTTGGGG
251.		CTATCATTCAGAAAATGTTGGC
252.	GATA-P18492(C)	GTATGGCAGTAGAGGGCATG
253.		AAGGTTACATTTCAAGAAATAAAGT
254.	GATA-P6915(C)	CTGTTCAGGCCTCAATATATACC
255.		AAGAGGATAGGTGGGGTTTG
256.	L19CA3	CCTCCCACCTAGACACAAT
257.		ATATGATCTTTGCATCCCTG
258.	L19PENTA1	AAGAAAGACCTGGAAGGAAT
259.		AAACAGCAAAACCTCATCTC
260.	L19TETRA5	CCACCACTTATTACCTGCAT
261.		TGAATGAATGAATGAACGAA
262.	LMP2	AACTGTGATTGTGCCACTGCACTC
263.		GTTTCTTCACCGCCTTTATCCCTCAAATG
264.	LMP3	GATGGGTGGAGGGCAGTTAAAG
265.		GTCAAGCAACTTGTCCAAGGCTAC
266.	LMP4	CAGGCTATCAGTTTCCTTTGGAG
267.		GGCAGGTAATACTGGAGAATTAGG
268.	LMP7	GACGGATCTCAGAGCCACTC
269.		GTTTCTTAAAAGATAAGGGCTTTTAAACC
270.	T18_5	AGTTTCACAGCTTGTTATGG
271.		GGTTGATGAAGTGAGACTTT
272.	T29_9	ATGGTGGATGCATCCTGTG
273.		GTTTCTTGTATTGACTCCTCCTCTGC
274.	774L	CAGTAAACAT
275.		TGTTGAGTGG
276.	774N	TCTCCTCAATGTGCATGT

277.		ATTCTACATA
278.	ASMI14	GTGTTTGCAT
279.		ACAAGTTGGC
280.	CA11_11	TAGTACCAGA
281.		TACATCCAAGAAAA

The source of marker was Sequana Therapeutics, Inc. unless a letter in parenthesis is indicated after the name, where G = Genethon; L = Nothen and Dewald (1995) Clin. Genet. **47**:165; U = the Utah genome center, see: The Utah Marker Development Group (1995) Am. J. Hum. Genet. **57**:619; c= the cooperative Human Lineage Center.

Table 1B

SEQ	Marker	Repeat and flanking sequence
282.	CA39_2	GAGACTCTGA(CA)nAATATATATA
283.	774F	TGTTGATCGC(CA)nAACCAAAATC
284.	774J	AATGCATGTA(TG)2TATA(TG)nGTGTGGTATG(TG)3TACATATGCG
285.	774O	CCTCCCAGAA(CA)n ATCATGATAA
286.	L19PENTA1	AGACAGTCTCAAAAAAT(ATTTT)nAAAGAAAAAGCTGGATAAAT
287.	65P14TE1	AACTAGCTTTAAGAAAATAAGAAGAAAAAGAAAGAAG(AAAG)2TAAG(AAAG)nAGAAAGAAAAG(AAAG)nAAAAG(AAAG)nAGGAATGATTGAC
288.	65P14	CGCGCACATA(CA)nCCCTTTCTCT
289.	774L	CAGTAAACAT(CA)n TGTTGAGTGG
290.	774N	TCTCCTCAATGTGCATGT (GTGC)2 ATGA (GTGC)2 (AC)n ATTCTACATA
291.	ASMI14	GTGTTTGCAT (GT)n T (GT)3 ACAAGTTGGC
292.	CA11_11	TAGTACCAGA (CA)2 CG(TG)2 (CA)2 GGCAAGCG (CA)n C (CA)3 TACATCCAAGAAAA

Genetic refinement of the ASTH1 region

The microsatellite markers isolated from YACs from the *ASTH1* region were genotyped in both the Tristan da Cunha and Toronto cohorts. Genetic refinement of the *ASTH1* region was accomplished by applying the transmission/disequilibrium test (TDT; Spielman *et al.* (1993) Am. J. Hum. Genet. **52**:506) to genetic data from the Tristan and Toronto populations, at markers throughout the ASTH1 region. The TDT statistic reflects the level of association between a marker allele and disease

status. A multipoint version of the TDT test controls for variability in heterozygosities between loci, and results in a smoother regional TDT curve than would a plot of single locus TDT data. Significance of a TDT value is determined by means of the χ^2 test; A χ^2 value of 3.84 or greater is considered statistically significant at a probability level of 0.05. Figure 1 shows graphs of χ^2 values for key ASTH1 region markers for both history of asthma with positive methacholine challenge, for the Toronto triad families. χ^2 is plotted vs. genomic location of the marker on the physical map.

The Toronto TDT peak is located at marker D11S2008 (χ^2= 11.6, $p < .0001$). The marker allele in disequilibrium is fairly rare (freq = 6%), representing the fourth most common allele at this marker. The relative risk of affection vs. normal for this allele is 5.25. This is also the peak marker for linkage and linkage disequilibrium in Tristan da Cunha, indicating that the ASTH1 gene is very close to this marker. The markers defining the limits of linkage disequilibrium were D11S907 and 65P14TE1. The physical size of the refined region is approximately 100 kb.

A significant TDT test reflects the tendency of alleles of markers located near a disease locus (also said to be in "linkage disequilibrium" with the disease) to segregate with the disease locus, while alleles of markers located further from the disease locus segregate independently of affection status. An expectation that derives from this is that a population for which a disease gene (*ie* a disease predisposing polymorphism) was recently introduced would show statistically significant TDT over a larger region surrounding the gene than would a population in which the mutant gene had been segregating for a greater length of time. In the latter case, time would have allowed more opportunity for markers in the vicinity of the disease gene to recombine with it. This expectation is fulfilled in our populations. The Tristan da Cunha population, founded only 10 generations ago, shows a broader TDT curve than does the set of Toronto families, which are mixed European in derivation and thus represent an older and more diverse, less recently established population.

Gene isolation and characterization

The tiling path of BACs, cosmids and PAC clones was subjected to exon trapping and cDNA selection to isolate sequences derived from ASTH1 region genes. Exon trap clones were isolated on the basis of size and ability to cross-hybridize. Approximately 300 putatively non-identical clones were sequenced. cDNA selection was performed with adult and fetal lung RNA using pools of tiling path clones. The cDNA selection clones were sequenced and the sequences assembled with those of the exon trap clones. Representative exon trapping clones spanning each assembly were chosen, and arranged as "masterplates" (96-well microtitre dishes) of clones. Exon trap masterplate clones and cDNA selection clones were subjected to expression studies.

Human multi-tissue Northern blots were probed with PCR products of masterplate clones. In some cases, exon trapping clones did not detect RNA species, either because they did not represent expressed sequences, or represented genes with very restricted patterns of expression, or due to small size of the exon probe.

Masterplate clones detecting discrete RNA species on Northern blots were used to screen lambda phage based cDNA libraries chosen on the basis of the expression pattern of the clone. The sequences of the cDNAs were determined by end sequencing and sequence walking. cDNAs were also isolated, or extended, by 5' and 3' rapid amplification of cDNA ends (RACE). In most cases, 5' RACE was necessary to obtain the 5' end of the cDNA.

ASTH1I and ASTH1J were detected by exon trapping. ASTH1I exons detected a 2.8 kb mRNA expressed at high levels in trachea and prostate, and at lower levels in lung and kidney. ASTH1I exons were used as probes to screen prostate, lung and testis cDNA libraries; positive clones were obtained from each of these libraries. Isolation of a ASTH1I cDNA clone from testis demonstrates that this gene is expressed in this tissue, and possibly others, at a level not detectable by Northern blot analysis.

ASTH1J exons detected a 6.0 kb mRNA expressed at high levels in the trachea, prostate and pancreas and at lower levels in colon, small intestine, lung and stomach. Pancreas and prostate libraries were screened with exon clones

from ASTH1J. cDNA clone end sequences were assembled using Sequencher (Alsbyte) with the sequences of the exon trapped clones, producing sequence contigs used to design sequence walking and RACE primers. The additional sequences produced by these methods were assembled with the original sequences to produce longer contigs of cDNA sequences. It was evident from the sequence assemblies that both ASTH1I and ASTH1J are alternatively spliced and/or have alternative transcription start sites at their 5' ends, since not all clones of either gene contained the same 5' sequence.

ASTH1J has three splice forms consisting of the alt1 form, found in prostate and lung cDNA clones, and in which the exons (illustrated in Figure 1) are found in the order: 5' a, b, c, d, e, f, g, h, i 3'. A second form, alt2, in which the exon order is: 5' a2, b, c, d, e, f, g, h, i 3' was seen in a pancreas cDNA clone. A third form, alt3, contains an alternate exon, a3, between exons a2 and b. The start codon is within exon b, so that the open reading frame is identical for the three forms, which differ only in the 5' UTR. The ASTH1J cDNAs shown as SEQ ID NO:2 (form alt1); SEQ ID NO:3 (form alt2); SEQ ID NO:4 (form alt3) are 5427, 5510 and 5667 bp in length, respectively. The sequence of the entire protein coding region and alternate 5' UTRs are provided. The 3' terminus, where the polyA tail is added, varies by 7 bp between clones. The provided sequences are the longest of these variants. The encoded protein product is provided as SEQ ID NO:5.

ASTH1I was seen in three isoforms denoted as alt1, alt2, and alt3. The exons of ASTH1I and ASTH1J were given letter designations before the directionality of the cDNA was known, the order is different for the two genes. In the alt1 form of ASTH1I, exons are in the following order: 5' i, f, e, d, c, b, a 3'. In the alt2 form of ASTH1I, an alternative 5' exon, j, substitutes for exon i, with the following exon arrangement: 5' j, f, e, d, c, b, a 3'. The alt3 form of the gene has the exon order: 5' f, k, h, g, e, d, c, b, a 3'. The alternative splicing and start codons in each of exons i, f and e give the three forms of ASTH1I protein different amino termini. The common stop codon is located in exon a, which also contains a long 3' UTR. Two polyadenylation signals are present in the 3' UTR; some cDNA clones end with a polyA tract just after the first polyA signal and for others the polyA tract is at the end of the sequence shown. Since the sequences shown for the alt1,

alt2, and alt3 forms of ASTH1I (2428 bp; 2280 bp and 2498 bp; respectively) are close to the estimated Northern blot transcript size of 2.8 kb, these sequences are essentially full length.

EST matches

The nucleotide sequences of the alt1, alt2 and alt3 forms of ASTH1J and the alt1, alt2 and alt3 forms of ASTH1I were used in BLAST searches against dbEST in order to identify EST sequences representing these genes. Perfect or near perfect matches were taken to represent sequence identity rather than relatedness. Accession numbers T65960, T64537, AA055924 and AA055327 represent the forward and reverse sequences of two clones which together span the last 546 bp (excluding the polyA tail) of the 3' UTR of ASTH1I. No ESTs spanned any part of the coding region of this gene. One colon cDNA clone (accession number AA149006) spanned 402 bp including the last 21 bp of the ASTH1J coding region and part of the 3' UTR.

Intron/exon structure determination

The genomic organization of genes in the ASTH1 region was determined by comparison by BLAST of cDNA sequences to the genomic sequence of the region. The genomic sequence of the ASHT1 region 5' to and overlapping ASTH1J, is provided in SEQ ID NO:1. Genomic structure of the ASTH1I and ASTH1J genes is shown in Figure 1; the intron/exon junction sequences are in Table 2.

TABLE 2: Genomic organization of the ASTH1I and ASTH1J genes.
*Exonic sequences are upper case, flanking sequences lower case.

SEQ NO	Exon	Size of exon (bp)	Sequences at the ends of and flanking the exons of ASTH1I and ASTH1J*
ASTH1I			
293.	i	>214	ggaggctgagCAGGGGTGCC...
294.			...ACTCCCACAGgtacctgcag
295.	j	>66	...CTGCCCTCACgtaagcgcct

296.	f	125	gctgttgcagGGTAATGTTG...
297.			...CATCAGACAGgtgcgtaca
298.	k	226	ggctggtgagGAGGGGCTGA...
299.			...CGCTCTGTGGgtgagcttca
300.	h	93	tgtggaatagCCCAATTACA...
301.			...AGGGTGCTGAgtgagtagta
302.	g	79	ttcttttcagGCCCTCGTGT...
303.			...TGCTGACCCGgtatggtggt
304.	e	232	tttggtgcagCCTGTGACTC...
305.			...CGCACACAAGgtcagtgttc
306.	d	51	tctttcccagGTTACTCCTT...
307.			...ATCAAAGACTgtaagtaacc
308.	c	69	tctatttcagATGCTGATTC...
309.			...AGTAGAACAAgtaagtgcag
310.	b	196	ttttcaaaagGCCTCCAAAG...
311.			...GAGCCCTGAGgtaagttaat
312.	a	1522	gcttttcagATACTACTAT...
313.			...TAACATGTTCaactgtctgt
314.	a	146	tgttatatgcATTTATCTTC...
315.			...GGTAAATGAGgtaagtcctg
316.	a2	229	tcttgttaagATCGCTCTCT...
317.			...CCTTGCCCAGgttctcttaa
318.	a3	157	gcaatcgcacCTGCACACCC...
319.			...ACTGCCCATTtctggtaaag
320.	b	100	cccctaacagATCATGATTC...
321.			...ACGTGCAATGgtaagagggc
322.	c	246	tgttttgcagTTTCCAGTGG...
323.			...AAGTGGAACGgtgactctct
324.	d	63	tccttcacagGCCAGTGCAG...

325.			...GAACAAACTGgtg agtagta
326.	e	69	tttttgtagAGCCTTCCAT...
327.			...AGCACAGTAGgtaactaact
328.	f	69	atggccacagATTTGTTGGA...
329.			...CTTCCTGTTGgtaagctgtc
330.	g	63	ttctccttagCAGAGTCACC...
331.			...AAAAAGCACAgtaagttggc
332.	h	196	ttttcatcagACCCGAGAGG...
333.			...GAGCTATGAGgtgaggagtt
334.	i	4457	tttgttacagATATTACTAC...
335.			...AGCCTGGAAAtgcgtgtttc

The deduced ASTH1I and ASTH1J proteins

The protein encoded by ASTH1J (SEQ ID NO:5) is 300 amino acids in length. A BLASTP search of the protein sequence against the public nonredundant sequence database (NCBI) revealed similarity to one protein domain of transcription factors of the *ets* family. The *ets* family, named for the E26 oncoprotein which originally defined this type of transcription factor, is a group of transcription factors which activate genes involved in a variety of immunological and other processes, or implicated in cancer. The family members most similar to ASTH1I and ASTH1J are: ETS1, ESX, ETS2, ELF, ELK1, TEL, NET, SAP-1, NERF and FLI. Secondary structure analysis and comparison of the protein sequence to the crystal structure of the human ETS1-DNA complex (Werner *et al.* (1995) Cell **83**:761) confirmed that it has a winged helix turn helix motif characteristic of some DNA binding proteins which are transcription factors.

Multiple sequence alignment of ASTH1I, ASTH1J, and other ETS-domain proteins detected a second, N-terminal domain shared by ASTH1I, ASTH1J and some, but not all, ETS-domain proteins. Conservation of this motif have been observed (Tei *et al.* (1992) Proc. Natl. Acad. Sci. USA **89**: 6856-6860), and its involvement in protein self-association have been documented for TEL, an ETS-domain protein, upon its fusion with platelet-derived growth factor β receptor (Carrol

et al. (1996) Proc. Natl. Acad. Sci. USA **93**:14845-14850). Alignment of the N-terminal conserved domain in the ETS proteins was converted into a generalized sequence profile to scan the protein databases using the Smith-Waterman algorithm. This search revealed that the N-terminal domain in ASTH1I, ASTH1J and other ETS-domain proteins belongs to the SAM-domain family (Schultz *et al.* (1997) Protein Science **6**:249-253). SAM domains are found in diverse developmental proteins where they are thought to mediate protein-protein interactions. Thus, both ASTH1I and ASTH1J are predicted to contain two conserved modules, the N-terminal protein interaction domain (SAM-domain) and the C-terminal DNA-binding domain (ETS-domain). The sequence segments between these two domains is predicted to have elongated, non-globular structure and may be hinges between the two functional domains in ASTH1I and ASTH1J.

The ASTH1I alt1 (SEQ ID NO:7), alt2 (SEQ ID NO:9) and alt3 (SEQ ID NO:11) forms are 265, 255 and 164 amino acids in length, respectively, and differ at their 5' ends. The ASTH1I and ASTH1J proteins show similarity to each other in the ets domain and between ASTH1J exon c and ASTH1I exon e. They are more related to each other than to other proteins. Over the *ets* domain they are 66% similar (*ie.* have amino acids with similar properties in the same positions) and 46% identical to each other. All three forms of ASTH1I have the helix turn helix motif located near the carboxy terminal end of the protein.

The alternate forms of the ASTH1I protein may differ in function in critical ways. The activity of *ets* transcription factors can be affected by the presence of independently folding protein structural motifs which interact with the *ets* protein binding domain (helix loop helix). The differing 5' ends of the ASTH1I proteins may help modulate activity of the proteins in a tissue-specific manner.

Polymorphism analysis of ASTH1I and ASTH1J

Affected and unaffected individuals from the Toronto cohort were used to determine sequence variants, as were approximately 25 controls derived from populations not selected for asthma. Affected and unaffected individuals from the Tristan da Cunha population were also chosen; the set to be assayed was also selected to represent all the major haplotypes for the ASTH1 region in that

population. This ensured that all chromosome types for Tristan were included in the analysis.

Polymorphism analysis was accomplished by three techniques: comparative (heterozygote detection) sequencing, radioactive SSCP and fluorescent SSCP. Polymorphisms found by SSCP were sequenced to determine the exact sequence change involved.

PCR and sequencing primers were designed from genomic sequence flanking each exon of the coding region and 5' UTRs of ASTH1I and ASTH1J. For fluorescent SSCP, the forward and reverse PCR primers were labeled with different dyes to allow visualization of both strands of the PCR product. In general, a variant seen in one strand of the product was also apparent in the other strand. For comparative sequencing, heterozygotes were also detected in sequences from both DNA strands.

Polymorphisms associated with the ASTH1I locus are listed in Table 3. The sequence flanking each variant is shown. Polymorphisms were also deduced from comparison of sequences from multiple independent cDNA clones spanning the same region of the transcripts, and comparison with genomic DNA sequence. The polymorphisms in the long 3' UTR regions of these genes were found by this method. One polymorphism in each gene is associated with an amino acid change in the protein sequence. An alanine/valine difference in exon c of ASTH1J is a conservative amino acid change. A serine/cysteine variant in exon g of ASTH1I is not a conservative change, but would be found only in the alt3 form of the protein.

The polymorphisms in the ASTH1I and J transcribed regions were genotyped in the whole Tristan da Cunha and Toronto populations, as well as in a larger sample of non-asthma selected controls, by high throughput methods such as OLA (oligonucleotide ligation assay; Tobe *et al.* (1996) Nucl. Acids Res. **24**:3728) or Taqman (Holland et al. (1992) Clin. Chem. 38: 462), or by PCR and restriction enzyme digestion. The population-wide data were used in a statistical analysis for significant differences in the frequencies of ASTH1I or ASTH1J alleles between asthmatics and non-asthmatics.

TABLE 3: POLYMORPHISMS IN THE ASTH1I AND ASTH1J GENES.

SEQ	Polymorphism Location	Sequence
	ASTH1I Transcribed region	
16.	EXON B (+)170	ACAGAATGACRTATGAAAAGT
17.	INTRON D (+)15	GTAACCAAGCKCAAGCCACCC
18.	INTRON F (+)24	AAGGAGCCCAYCTGAGTGCAG
19.	EXON G (+)62 ser→cys	CGTTCCATCTSTGCTCTGTGC
20.	EXON H (+)77	AGCGCCTCGGYTGGCTGAGGG
21.	EXON A 3' UTR (+)1176	TGTATTCAAGYGCTATAACAC
22.	EXON I (+)76	CACTGAGAAGCCC/-ACAGGCCTGT
23.	EXON I (+)86	CCCACAGGCCWGTCCCTCCAA
24.	INTRON J (+)93	CGTCCATCTCYAGCTCCAGGG
	ASTH1J Transcribed region	
25.	EXON A 5' UTR (+)38	GACTTGATAAYGCCCGTGGTG
26.	EXON A 5' UTR (+)39	ACTTGATAACRCCCGTGGTGC
27.	EXON A 5' UTR (+)99	CTCCCCTCCAWGAGCCACAGC
28.	INTRON A (+) 224/225	ATTTCCTGCATT/-GTCTGGACTT
29.	INTRON A (+)48	ATCCAAACACYTGAGTGGAAA
30.	EXON A3 (+)28	AGTTTCCTCARTGCGGGAGCT
31.	EXON C (+)158	GCGAGCACCTYTGCAGCATGA
32.	EXON C (+)190 ala→val	TTCACCCGGGYGGCAGGGACG
33.	INTRON D (-)36/37	CTGGGGAAAA(GA)/TGATCGCTGAC
34.	INTRON F (-)22	GTCAATTAAAYGGCTCTCATT
35.	INTRON G (-)27	TAGATCATTCRTAACCTGCCT
36.	EXON I (3' UTR) (+)22	AAAGAGAAATWCTGGAGCGTG
37.	EXON I (3' UTR) (+)220	ATGAGGGGAAMAAGAAACTAC
38.	EXON I (3' UTR) (+)475	TTTTGTATGTKACATGATTTA
39.	EXON I (3' UTR) (+)871	AGCTTGGTTCYTTTTTGCTCC
40.	EXON I (3' UTR) (+)1084	TTGACACCAGRAACCCCCCAG
	5' to ASTH1J	
41.	CAAT box -165	AAATGAGCCARTGTTTGTAAT

42.	5PW1J_P01+399	ATCCATTTTGYATTCCTCATT
43.	5PW1J_P01+1604	CTGGAGCTCARACCAGACAGC
44.	5PW1J_P02+1382	GCCAGTGCAGSCATCATTACC
45.	5PW1J_P03+128	AGTTCAAATCRTAATTTTTAT
46.	5PW1J_P03+556	TCATCAGAATYTAAATCTCCC
47.	5PW1J_P03+712	GGAGATTCAGA/-TGAAGCAAGA
48.	5PW1J_P03+781	TTTTTCCACAYCCAGCCTGGC
49.	5PW1J_P03+791	CCCAGCCTGGYGAACCCTGGC
50.	5PW1J_P03+820	CTCTTCATCAYGGTCAAATAC
51.	5PW1J_P03+1530	CAACTTGCTGYCAAAGTGCTG
52.	5PW1J_P03+1605	TACTATGTGCYAGATACTAAG
53.	5PW1J_P04+542/543	ATGCCACTTTRRACAACTTGAG
54.	5PW1J_P04+973	CGCATGCCTGKAAAGAAGAGA
55.	5PW1J_P04+1079	GGATAAGCACMAGTGAGCCTG
56.	5PW1J_P04+1153	AAAGCCAGACRGCAACTTGTG
57.	5PW1J_P04+1430	TCTCAAAAAGRGTGATAGGAG
58.	5PW1J_P05+334	TCTGAATCCTSTCTCCTCCTT
59.	5PW1J_P05+749	TAGAACCAGGWTGTGGGACCA
60.	5PW1J_P05+915	TTCTTGTGTCRGGCGCAAAAC
61.	5PW1J_P06+529	AACCAACATGRAGAAACCCCA
62.	5PW1J_P06+1290	AATAAACTATRGTTCACCTAG
63.	5PW1J_P06+1573	ACATATTTGTRTCTCATATGA
64.	5PW1J_P06+1661	CAAAGCAGTTYCTAATAATCC
65.	5PW1J_P07+335	AGATCCTAACYGGGGCCTCCT
66.	5PW1J_P07+731	CTCTTTCTCTYTGCTTCCTCC
67.	5PW1J_P07+1024	TTAGGAATCCWCAAATATGTA
68.	5PW1J_P07+1610	GTCTGACTCCRCCTCCCTCAT
69.	5PW1J_P08+398	GAATCACATCRTGAGAAATGT
70.	5PW1J_P08+439	AATTCAATCCYTCACAGACTT
71.	5PW1J_P08+580	GTGTAGCCAGRGTTGCTAATT
72.	5PW1J_P08+762	CCTAGAAATASCCAAGGGCAC
73.	5PW1J_P08+952	AAATTCTCATRCCTCACCCTC
74.	5PW1J_P08+1172	TCCCACCCCTRTCACCTTCAT
75.	5PW1J_P08+1393	CCTCATTCTCRGAAGCCAACA
76.	5PW1J_P08+1433	GAAGAGCCGTYCAGTCCCTTT
77.	5PW1J_P08+1670	TCCATAGGCTYTTTATTTGGC
78.	5PW1J_P08+1730	TCGTTTAGTAYACAGGCTTTG
79.	5PW1J_P09+59	GCCTCAGTTGYCCCAGCTATA
80.	5PW1J_P09+145	AGCAAAATGCWCTATGCACTG
81.	5PW1J_P09+892	GTGTCCTGAC(TTGCACTCCAC)/-ACACTGCCTG
82.	5PW1J_P10+1070	ATCAGATAACRCCTACACTTA
83.	5PW1J_P10+1511	TCTCTCTTCTSCCTGCCCTGT
84.	5PW1J_P09+1132	TGGACACAGGKAGGGGAATAT

85.	5PW1J_P09+1688	TGTCACTTGCRCATACAAGGC
86.	5PW1J_P09+1900	ATCATCAGATYAGCCCAGAAT
87.	5PW1J W1R1-1060	TCAACAGAGARAGTTAATGGT
88.	5PW1J W1R1-1831	AGCAATAATGYTTCCCTTTTC
89.	5PW1J W1R1-2355	TCTAGCTTTTYTGTGTTTTTT
90.	5PW1J W1R1-3160	GATTCCTTAAYGCTTGATACT
91.	5PW1J W1R1-3787	CCTCCTCCAGYACCAAAGTGG
92.	W1J_CD+24	ATGGCCACAGRTCAAATCCTG
93.	W1J_CA+564	ACTGAGTGTTYATGCCAATTT
	5' to ASTH1I	
94.	WI_CL+94	GACAAGCCCTRTCTGACACAC
95.	WI_CN+134	TGAAAAGCCTYCTTGCTGCCT
96.	WI_CQ-28	TCCTGGAGTTYCTTTGCTCCC
97.	WI_CQ+39	GATTCCAAATWAACTAAAGAT
98.	P14-16+191662	GACCTCAAGTCRTCCACCCGCC
99.	P14-16+192592	AACAAATACTMCCCCGCAACCC
100.	P14-16+192762	ATTTTTTTTTT/-AAGGAAAATA
101.	P14-16+195066	AAATTTCCCCMAAACAAGCAG
102.	P14-16+196590	GAGAAAGGGTRTGTGTGTGTG
103.	P14-16+196617	GTGTGTGTGTGT-/GTGTATGTGCGCGTG
104.	P14-16+196902	ATCGGGAACCYCATACCCCAA
105.	P14-16+198040	TTTGTTTCGCMATGAGGTACG
106.	P14-16+198240	TGAGGGTGTTSTGGGCTGGAC
107.	P14-16+198840	TCTTCATTGGYATCTGAATGT
108.	P14-16+200120	GCGAGCACCTYTGCAGCATGA
109.	P14-16+200617	AACCCCCCCCMCACACACACA
110.	J5-16+4454	TCAGTGCTCTSTAATCAGTCA
111.	J5-16+4825	TCTTTGTGAAA-/(GA)AATTAGTCTG*
112.	J5-16+5426	GCTGCCCTGASAGCTGGGCCA
113.	J5-16+5623	CCTTCTGATCYTTGTTTGCTG
114.	J5-16+7386	GGAACACTGAKTCTTGATTAG
115.	J5-16+7904	TAGGCTTCTCYTGATAATTGA
116.	J5-16+8055	TCTTAAAATAMTTGGCTTGTA
117.	J5-16+10595	TAGATCATTARTAACCTGCCT
118.	J5-16+11140	ATGAGGGGAAMAAGAAACTAC
119.	J5-16+12004	TTGACACCAGRAACCCCCCAG
120.	J5-16+12219	TGTTTTAAATRTTAGGGACAA
121.	J5-16+12303	GTAAGCATAGYAATGTAGCAG
122.	J5-16+13504	GGCTCTTTCTKCAACCTTTCC
123.	J5-16+14120	GACCCAGGTTRTGAGTTTTCC
124.	ASTH1I, exon B +169	GACAGAATGAYATATGAAAAG
125.	ASTH1I, exon I +69	TGTGTGACACYGAGAAGCCCA

126.	ASTH1J, exon C +56	AGTACTGGACMAAGTACCAGG
127.	5' ASTH1J, WI_Cg -9	CCTGGGAGCARGTATTGCATT
	ASTH1J Intron A	
128.	WIJ_Ia01 +39	AGATTTGAGGYCTCAGGTCCC
129.	WIJ_Ia01 +140	TGTCAATGTCRCATGATAAGC
130.	WIJ_Ia01 +678	TTGCCCCAGTKTTCTCCGGGC
131.	WIJ_Ia01 +855	TATGAGCAGCRTAGGGAGTGG
132.	WIJ_Ia01 +929	AGTTGACTGA(AAAA)/-TAAATAAGAC
133.	WIJ_Ia 03 +362	ATTCAAATAGSCTCTAGAAAC
134.	WIJ_Ia 03 +918	CCCAGAATTTMATATCCATTC
135.	WIJ_Ia 03 +943	TGACCCAACARAAACTCACTG
136.	WIJ_Ia 03 +1569	CCAGAATATAWCATCAGCCCT
137.	WIJ_Ia 03 +1580	CATCAGCCCTWCTGAGGAGAT
138.	WIJ_Ia 02 +435	CCAGAACAGAYTTTATTCTGT
139.	WIJ_Ia 02 +583	TTCAGCCATCYTTCCAGTTGT
140.	WIJ_Ia 02 +643	TCACTAACTCWAAAACGACAT
141.	WIJ_Ia 02 +648	AACTCAAAAAYGACATCCTCC
142.	WIJ_Ia 02 +1048	GAACTGCACARGTTGCACACT
143.	WIJ_Ia 02 +1061	TTGTTCCATGSACTACCTCCT
144.	WIJ_Ia 02 +1142	ACAGCAGGCAYTCAACAAATT
145.	WIJ_Ia 04 +410	TTATTTTTGGSTTTGTTTTAA
146.	WIJ_Ia 04 +1056	TAGGCTGTTCYCTGCCATCAC
147.	WIJ_Ia 05 +1484	GTGCTCTGGGMCACACAGCTC
148.	WIJ_Ia 05 +1103	AGACCCGATARGAGCTCCTTC
149.	WIJ_Ia 05 +1823	CATCTTGCGCRGTCATGTAAG
150.	WIJ_Ia 05 +1852	CAGCACAGCTRTTCCCTCAAA
151.	WIJ_Ia 05 +1906	TTTGGAAACAYGGTGAAGTAT
152.	WIJ_Ia 05 +1913	ACACGGTGAARTATTGTCTCC
153.	WIJ_Ia 06 +794	AAAAGTGGATMCTCTGCAAAC
154.	WIJ_Ia 06 +814	CTTCAAATGCRGCTATTAAAG
155.	WIJ_Ia 06 +1197	CCTGGGAGCAYGGTAAATCAG
156.	WIJ_Ia 06 +1231	TGAAAATGTCRCTTTCTCACCT
157.	WIJ_Ia 06 +1256	CCTGATATTTRCCAACAAGAA
158.	WIJ_Ia 06 +1535	AAAGGGTTAGYTTGTCCCCTT
159.	WI_Caa +163	TGAAAATAAAASACAATTTTTT

The sequences are listed with the variant residues represented by the appropriate single letter designation, *i.e.* A or G is shown by "R". The variant residues are underlined. Where the polymorphism is a deletion, the underlined residues are underlined, and the alternative form shown as a "-".

[a]Where intron 'a' is the intron 3' to exon 'a', etc.

[b]Position numbers correspond to the position within the intron or exon, with nucleotide +1 being the 5'-most base of the exon or the intron. Alternatively, negative numbers denote the number of bases from the 3' end of an intron.

[c]Position in cDNA = position # for the exon a form of ASTH1J or the exon i form of ASTH1I.

[d]Exonic sequences are uppercase, intronic sequences lower case.
UTR = untranslated region. N/A = not applicable.

Cross-species sequence conservation

Cross-species sequence conservation can reveal the presence of functionally important areas of sequence within a larger region. Approximately 90 kb of sequence lie between ASTH1I and ASTH1J, which are transcribed in opposite directions (Figure 1). The transcriptional orientation of these genes may allow coordinate regulation of their expression. The expression patterns of these genes are similar but not identical. Sequences found 5' to genes are critical for expression. To search for regulatory or other important regions, the genomic sequence between ASTH1I and ASTH1J, was examined and plasmid clones derived from genomic sequencing experiments chosen for cross-species hybridization experiments. The criterion for probe choice was a lack of repeat elements such as Alu or LINEs. Inserts from these clones were used as probes on Southern blots of EcoRI-digested human, mouse and pig or cow genomic DNA. Probes that produced discrete bands in more than one species were considered conserved.

Conserved probes clustered in four locations. One region was located 5' to ASTH1I and spanned exon j of this gene. A second conserved region was located 5' to ASTH1IJ, spanning approximately 10 kb and beginning 6 kb 5' to ASTH1J exon a (and is within SEQ ID NO:1). Two other clusters of conserved probes were noted in the region between ASTH1I and J. They are approximately 10 and 6 kb in length.

Promoters, enhancers and other important control regions are generally found near the 5' ends of genes or within introns. Methods of identifying and characterizing such regions include: luciferase assays, chloramphenicol acetyl transferase (CAT) assays, gel shift assays, DNAseI protection assays (footprinting), methylation interference assays, DNAseI hypersensitivity assays to detect functionally relevant chromatin-ree regions, other types of chemical protection assays, transgenic mice with putative promoter regions linked to a reporter gene such as β-galactosidase, *etc*. Such studies define the promoters and other critical

control regions of ASTH1I and ASTH1J and establish the functional significance of the evolutionarily conserved sequences between these genes.

Discussion

The ASTH1 locus is associated with asthma and bronchial hyperreactivity. ASTH1I and ASTH1J are transcription factors expressed in trachea, lung and several other tissues. The main site of their effect upon asthma may therefore be in trachea and lung tissues. Since *ets* family genes are transcription factors, a function for ASTH1I and ASTH1J is activation of transcription of particular sets of genes within cells of the trachea and lung. Cytokines are extracellular signalling proteins important in inflammation, a common feature of asthma. Several *ets* family transcription factors activate expression of cytokines or cytokine receptors in response to their own activation by upstream signals. ELF, for example, activates IL-2, IL-3, IL-2 receptor α and GM-CSF, factors involved in signaling between cell types important in asthma. NET activates transcription of the IL-1 receptor antagonist gene. ETS1 activates the T cell receptor α gene, which has been linked to atopic asthma in some families (Moffatt *et al.* (1994) *supra.*)

Activation of genes involved in inflammation by other members of the *ets* family suggest that the effect of these ASTH1 genes on development of asthma is exerted through influencing cytokine or receptor expression in trachea and/or lung. Cytokines are produced by structural cells within the airway, including epithelial cells, endothelial cells and fibroblasts, bringing about recruitment of inflammatory cells into the airway.

A model for the role of ASTH1I and ASTH1J in asthma that is consistent with the phenotype linked to ASTH1, the expression pattern of these genes, the nature of the ASTH1I/J genes, and the known function of similar genes is that aberrant function of ASTH1I and/or ASTH1J in trachea or lung leads to altered expression of factors involved in the inflammatory process, leading to chronic inflammation and asthma.

Functional analysis of a ASTH1J promoter sequence variant and location of the ASTH1J promoter

Primer extension analyses performed using total RNA isolated from both bronchial and prostate epithelial cells have revealed one major and five minor transcription start sites for ASTH1J. The major site accounts for more than 90% of ASTH1J gene transcriptional initiation. None of these sites are found when the primer extension analysis is performed using mRNA isolated from human lung fibroblasts that do not express ASTH1J.

Identification of the ASTH1J transcriptional start site has allowed the localization of a putative TATA box (TTTAAAA) between positions -24 and -30 (24 to 30 bp 5' to the transcription start site). Although the sequence is not that of a typical TATA box, it conforms to the consensus sequence (TATAAAA) for TATA box protein binding as compared with 389 TATA elements (Transfac database: http://transfac.gbf-braunschweig.de/, ID: V$TATA_01).

Analysis of the CAAT box "G" polymorphism by gel shift assay

Binding of nuclear proteins to a polymorphism in the GCCAAT motif (GCCAAT or GCCAGT) found at position -140 (140 bp 5' to the transcription start of ASTH1J as defined by primer extension experiments, previously referred to as "-165 bp"), has been assessed using electrophoretic mobility shift assays. These experiments clearly showed a remarkable difference when binding of nuclear proteins to radioactively-labelled double stranded oligonucleotides containing the normal "A" vs the mutant "G" nucleotide was examined. A specific set of nuclear proteins was able to bind to the normal oligonucleotide, but did not bind to the "G" oligonucleotide. The specificity of the DNA binding complexes was further addressed by competition with either normal or mutant unlabeled oligonucleotides. Addition of increasing amounts of normal unlabeled oligonucleotide effectively competed binding of nuclear proteins to the labeled normal oligonucleotide, while the addition of increasing amounts of unlabelled "G" oligonucleotide did not.

The GCCAAT cis-element is found in many promoters at various locations relative to genes, as well as in distal enhancer elements. There is no known correlation between location of these elements and activity. Both positive and

negative regulatory trans-acting factors are known to bind this class of cis element. These factors can be grouped into the NF-1 and C/EBP families.

The nuclear factor-1 (NF-1) family of transcription factors comprises a large group of eukaryotic DNA binding proteins. Diversity within this gene family is contributed by multiple genes (including: NF-1A, NF-1B, NF-1C and NF-1X), differential splicing and heterodimerization.

Transcription factor C/EBP (CCAAT-enhancer binding protein) is a heat stable, sequence-specific DNA binding protein first purified from rat liver nuclei. C/EBP binds DNA through a bipartite structural motif and appears to function exclusively in terminally differentiated, growth arrested cells. C/EBPα was originally described as NF-IL-6; it is induced by IL-6 in liver, where it is the major C/EBP binding component. Three more recently described members of this gene family, designated CRP 1, C/EBP β and C/EBP δ, exhibit similar DNA binding specificities and affinities to C/EBP α. Furthermore, C/EBP β and C/EBP δ readily form heterodimers with each other as well as with C/EBP α.

Members of the C/EBP family of transcription factors, but not members of the NF-1 family, bind to the ASTH1J promoter region, as determined by the use of commercially available antibodies (Santa Cruz Biotechnologies, Santa Cruz, CA) that recognize all NF-1 and C/EBP family members known to date, in electrophoretic mobility shift assays.

Fabricating a DNA array of polymorphic sequences

DNA array: is made by spotting DNA fragments onto glass microscope slides which are pretreated with poly-L-lysine. Spotting onto the array is accomplished by a robotic arrayer. The DNA is cross-linked to the glass by ultraviolet irradiation, and the free poly-L-lysine groups are blocked by treatment with 0.05% succinic anhydride, 50% 1-methyl-2-pyrrolidinone and 50% borate buffer.

The spots on the array are oligonucleotides synthesized on an ABI automated synthesizer. Each spot is one of the alternative polymorphic sequences indicated in Tables 3 to 8. For each pair of polymorphisms, both forms are included. Subsets include (1) the *ASTH1J* polymorphisms of Table 3, (2) the

ASTH1I polymorphisms of Table 3; and (3) the polymorphisms of Table 4. Some internal standards and negative control spots including non-polymorphic coding region sequences and bacterial controls are included.

Genomic DNA from patient samples is isolated, amplified and subsequently labeled with fluorescent nucleotides as follows: isolated DNA is added to a standard PCR reaction containing primers (100 pmoles each), 250uM nucleotides, and 5 Units of Taq polymerase (Perkin Elmer). In addition, fluorescent nucleotides (Cy3-dUTP (green fluorescence) or Cy5-dUTP (red fluorescence), sold by Amersham) are added to a final concentration of 60 uM. The reaction is carried out in a Perkin Elmer thermocycler (PE9600) for 30 cycles using the following cycle profile: 92°C for 30 seconds, 58°C for 30 seconds, and 72°C for 2 minutes. Unincorporated fluorescent nucleotides are removed by size exclusion chromatography (Microcon-30 concentration devices, sold by Amicon).

Buffer replacement, removal of small nucleotides and primers and sample concentration is accomplished by ultrafiltration over an Amicon microconcentrator-30 (mwco = 30,000 Da) with three changes of 0.45 ml TE. The sample is reduced to 5 µl and supplemented with 1.4 µl 20X SSC and 5 µg yeast tRNA. Particles are removed from this mixture by filtration through a pre-wetted 0.45µ microspin filter (Ultrafree-MC, Millipore, Bedford, Ma.). SDS is added to a 0.28% final concentration. The fluorescently-labeled cDNA mixture is then heated to 98°C for 2 min., quickly cooled and applied to the DNA array on a microscope slide. Hybridization proceeds under a coverslip, and the slide assembly is kept in a humidified chamber at 65°C for 15 hours.

The slide is washed briefly in 1X SSC and 0.03% SDS, followed by a wash in 0.06% SSC. The slide is kept in a humidified chamber until fluorescence scanning was done.

Fluorescence scanning and data acquisition. Fluorescence scanning is set for 20 microns/pixel and two readings are taken per pixel. Data for channel 1 is set to collect fluorescence from Cy3 with excitation at 520 nm and emission at 550-600 nm. Channel 2 collects signals excited at 647 nm and emitted at 660-705 nm, appropriate for Cy5. No neutral density filters are applied to the signal from either channel, and the photomultiplier tube gain is set to 5. Fine adjustments are then

made to the photomultiplier gain so that signals collected from the two spots are equivalent.

Construction of an asth1J Transgenic Mouse

Isolation of mouse asth1-J genomic fragment:

Phage MW1-J was isolated by screening a mouse 129Sv genomic phage library (Stratagene) with the 443bp BamHI-SmaI fragment from the 5' region of the human asth1-J cDNA clone PA1001A as probe. The 23kb insert in MW1-J was sequenced.

Assembly of asth1-Jexb targeting construct:

A 2.65kb SacI fragment (bp7115-bp9765) from MW1-J was isolated, cloned into the SacI site of pUC19, isolated from the resultant plasmid as an EcoRI-XbaI fragment, inserted into the EcoRI-XbaI sites of pBluescriptII KS+ (Stratagene), and the 2.5kb XhoI-MluI fragment isolated. A 5.4kb HindIII fragment (bp11515-bp16909) was isolated from MW1-J, inserted into the HindIII site of pBluescriptII KS+, reisolated as a XhoI-NotI fragment, inserted into the XhoI-NotI sites of pPNT, and the 9.5kb XhoI-MluI fragment isolated. The two XhoI-MluI fragments were ligated together to produce the final targeting construct plasmid, asth1exb. Asth1exb was linearized by digestion with NotI and purified by CsCl banding.

Identification of targeted ES clones:

Approximately 10 million RW4 ES cells (Genome Systems) were electroporated with 20 μg of linearized asth1exb and grown on mitomycin C inactivated MEFs (Mouse Embryo Fibroblasts) in ES cell medium (DMEM + 15% fetal bovine serum+1000U/ml LIF (Life Technologies)) and 400 μg/ml G418. After 24-48hrs, the cells were refed with ES cell medium. After 7-10 days in selection culture approximately 200 colonies were picked, trypsinized, grown in 96 well microtiter plates, and expanded in duplicate 24 well microtiter plates. Cells from one set of plates were trypsinized, resuspended in freezing medium (Joyner, A., ed., Gene Targeting, A Practical Approach. 1993. Oxford University Press), and stored at -85C. Genomic DNA was isolated from the other set of plates by standard

methods (Joyner, *supra.*) Approximately 10 μg of genomic DNA per clone were digested with NdeI and screened by southern blotting using a 100 bp fragment (bp6164-bp6260) as probe. A banding pattern consistent with targeted replacement by homologous recombination at the asth1-J locus was detected in 10 of 113 clones screened.

Production of asth1-J knockout mice:

Two of the targeted clones, cl#117 and cl#58, were expanded and injected into C57BL/6 blastocysts according to standard methods (Joyner, *supra*). High percentage male chimeric founder mice (as ascertained by extent of agouti coat color contribution) were bred to A/J and C57BL/6 female mice. Germline transmission was ascertained by chinchilla or albino coat color offspring from A/J outcrosses and by agouti coat color offsprint from C57BL/6 outcrosses. The NdeI southern blot assay employed for ES cell screening was used to identify germline offspring carrying the targeted allele of Asth1-J. Germline offspring from both A/J and C57BL/6 outcrosses were identified and bred with A/J or C57BL/6 mates respectively..

Mice heterozygous for the Asth1-J targeted allele are interbred to obtain mice homozygous for the asth1-J targeted allele. Homozygotes are identified by NdeI Southern blot screening described above. The germline offspring of the chimeric founders are 50% A/J or C57BL6 and 50% 129SvJ in genetic background. Subsequent generations of backcrossing with wild type A/J or C57BL/6 mates will result in halving of the 129SvJ contribution to the background. The percentage A/J or C57BL/6 background is calculated for each homozygous mouse from its breeding history.

Molecular and cellular analysis of homozygous mice:

Various tissues of homozygotes, heterozygotes and wild type littermates at various stages of development from embryonic stages to mature adults are isolated and processed to obtain RNA and protein. Northern and western expression analyses as well as *in situ* hybridizations and immunohistochemical analyses are

performed using cDNA probes and polyclonal and/or monoclonal antibodies specific for asth1-J protein.

Phenotypic analysis of homozygous mice:

A/J, C57BL/6, wild type, heterozygous and homozygous mice in both A/J and C57BL/6 backgrounds at varying stages of development are assessed for gross pathology and overt behavioral phenotypic differences such as weight, breeding performance, alertness and activity level, etc.

Metacholine challenge tests are performed according to published protocols (De Sanctis *et al.* (1995). Quantitative Locus Analysis of Airway Hyperresponsiveness in A/J and C57BL/6J mice. Nat. Genet. **11**:150-154.).

Targeting at asth1-J exon C:

Assembly of exon C targeting construct:

A 3.2kb HindIII-XbaI fragment (bp11515-bp14752) from MW1-J was isolated, cloned into the HindIII-XbaI site of pUC19, isolated from the resultant plasmid as a KpnI-XbaI fragment, inserted into the KpnI-XbaI sites of pBluescriptII KS+ (Stratagene), and the 4.5kb RsrII-MluI fragment isolated. A 3.4kb HindIII fragment (bp17217-bp20622) was isolated from MW1-J, inserted into the HindIII site of pBluescriptII KS+, reisolated as a XhoI-NotI fragment, inserted into the XhoI-NotI sites of pPNT, and the 9.5kb RsrII-MluI fragment isolated. The two RsrII-MluI fragments were ligated together to produce the final targeting construct plasmid, Asth1exc. Asth1exc was linearized by digestion with NotI and purified by CsCl banding.

Identification of targeted ES clones:

Approximately 10 million RW4 ES cells (Genome Systems) were electroporated with 20µg of linearized asth1exc and grown on mitomycin C inactivated MEFs (Mouse Embryo Fibroblasts) in ES cell medium (DMEM + 15% fetal bovine serum+1000U/ml LIF (Life Technologies)) and 400 µg/ml G418. After 24-48hrs, the cells were refed with ES cell medium. After 7-10 days in selection culture approximately 200 colonies were picked, trypsinized, grown in 96 well

microtiter plates, and expanded in duplicate 24 well microtiter plates. Cells from one set of plates were trypsinized, resuspended in freezing medium (Joyner, *supra*), and stored at -85C. Genomic DNA was isolated from the other set of plates by standard methods (Joyner, *supra*). Approximately 10 µg of genomic DNA per clone were digested with NcoI and screened by southern blotting using a 518bp fragment (bp8043-bp8560) as probe. A banding pattern consistent with targeted replacement by homologous recombination at the Asth1-J locus was detected in 3 of 46 clones screened.

Targeted clones are injected into blastocysts and high percentage chimeras bred to A/J and C57BL/6 mates analogously to that done for asth1-Jexb knockout mice. Heterozygote, homozygote and wild type littermates are obtained and analyzed analogously to that done for asth1-Jexb knockout mice.

The data presented above demonstrate that ASTH1I and ASTH1J are novel human genes linked to a history of clinical asthma and bronchial hyperreactivity in two asthma cohorts, the population of Tristan da Cunha and a set of Canadian asthma families. A TDT curve in the ASTH1 region indicates that ASTH1I and ASTH1J are located in the region most highly associated with disease. The genes have been characterized and their genetic structure determined. Full length cDNA sequence for three isoforms of ASTH1I and three isoforms of ASTH1J are reported. The genes are novel members of the *ets* family of transcription factors, which have been implicated in the activation of a variety of genes including the TCRα gene and cytokine genes known to be important in the aetiology of asthma. Polymorphisms in the ASTH1I and ASTH1J genes are described. These polymorphisms are useful in the presymptomatic diagnosis of asthma susceptibility, and in the confirmation of diagnosis of asthma and of asthma subtypes.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT: AxyS Pharmaceuticals, Inc.

(ii) TITLE OF THE INVENTION: Asthma Related Genes

(iii) NUMBER OF SEQUENCES: 339

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Bozicevic & Reed, LLP
(B) STREET: 285 Hamilton Ave, Suite 200
(C) CITY: Palo Alto
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 94301

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 21-JAN-1998
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sherwood, Pamela J
(B) REGISTRATION NUMBER: 36,677
(C) REFERENCE/DOCKET NUMBER: SEQ-4P

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650-327-3231
(B) TELEFAX: 650-327-3231
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72928 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5427 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 5510 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5667 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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ATCGCTCTCT GGTAGAGTTG ACGTGACACT CATTTCTGTT GTGGGTGGGG CCCTGGTTGG     60
GAGGCATTGG CTCCACTGCA GCCTGGGTGT CTAGAGACCA CATTCTCACC CTGCCTTTGT    120
TACTGGGAAA CCGAACGCGG CGCTGTGGCT TTCAGCTTGG GTAAGCCGGG TCTGCGGCGG    180
GGATTGCCAT CTGAAGACAG AGGCAGGAGG GCAGCCACAC CTTGCCCAGC TGCACACCCA    240
GTAACAAGTT TCCTCAGTGC GGGTATCTGC CACAGGCTGG GCTGGTCATC AAAGGGCCTC    300
AGTCATATTT TAATAGAGCT CTTCAAGTAT CTGGCTTTGT GATAATATCA GGAATCAGTT    360
GGTTTCTCTG ACAGACACTG CCCATTATCA TGATTCTGGA AGGAGGTGGT GTAATGAATC    420
TCAACCCCGG CAACAACCTC CTTCACCAGC CGCCAGCCTG GACAGACAGC TACTCCACGT    480
GCAATGTTTC CAGTGGGTTT TTTGGAGGCC AGTGGCATGA AATTCATCCT CAGTACTGGA    540
CCAAGTACCA GGTGTGGGAG TGGCTCCAGC ACCTCCTGGA CACCAACCAG CTGGATGCCA    600
ATTGTATCCC TTTCCAAGAG TTCGACATCA ACGGCGAGCA CCTCTGCAGC ATGAGTTTGC    660
AGGAGTTCAC CCGGGCGGCA GGGACGGCGG GGCAGCTCCT CTACAGCAAC TTGCAGCATC    720
TGAAGTGGAA CGGCCAGTGC AGTAGTGACC TGTTCCAGTC CACACACAAT GTCATTGTCA    780
AGACTGAACA AACTGAGCCT TCCATCATGA ACACCTGGAA AGACGAGAAC TATTTATATG    840
ACACCAACTA TGGTAGCACA GTAGATTTGT TGGACAGCAA AACTTTCTGC CGGGCTCAGA    900
TCTCCATGAC AACCACCAGT CACCTTCCTG TTGCAGAGTC ACCTGATATG AAAAAGGAGC    960
AAGACCCCCC TGCCAAGTGC CACACCAAAA AGCACAACCC GAGAGGGACT CACTTATGGG   1020
AATTCATCCG CGACATCCTC TTGAACCCAG ACAAGAACCC AGGATTAATA AAATGGGAAG   1080
ACCGATCTGA GGGCGTCTTC AGGTTCTTGA AATCAGAGGC AGTGGCTCAG CTATGGGGTA   1140
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AAAAGAAGAA CAACAGCAGC ATGACCTATG AAAAGCTCAG CCGAGCTATG AGATATTACT 1200
ACAAAAGAGA AATACTGGAG CGTGTGGATG GACGAAGACT GGTATATAAA TTTGGGAAGA 1260
ATGCCCGAGG ATGGAGAGAA AATGAAAACT GAAGCTGCCA ATACTTTGGA CACAAACCAA 1320
AACACACACC AAATAATCAG AAACAAAGAA CTCCTGGACG TAAATATTTC AAAGACTACT 1380
TTTCTCTGAT ATTTATGTAC CATGAGGGGA AAAAGAAACT ACTTCTAACG GGAAGAAGAA 1440
ACACTACAGT CGATTAAAAA AATTATTTTG TTACTTCGAA GTATGTCCTA TATGGGGAAA 1500
AAACGTACAC AGTTTTCTGT GAAATATGAT GCTGTATGTG GTTGTGATTT TTTTTCACCT 1560
CTATTGTGAA TTCTTTTTCA CTGCAAGAGT AACAGGATTT GTAGCCTTGT GCTTCTTGCT 1620
AAGAGAAAGA AAAACAAAAT CAGAGGGCAT TAAATGTTTT GTATGTGACA TGATTTAGAA 1680
AAAGGTGATG CATCCTCCTC ACATAAGCAT CCATATGGCT TCGTCAAGGG AGGTGAACAT 1740
TGTTGCTGAG TTAAATTCCA GGGTCTCAGA TGGTTAGGAC AAAGTGGATG GATGCCGGGA 1800
AGTTTAACCT GAGCCTTAGG ATCCAATGAG TGGAGAATGG GGACTTCCAA AACCCAAGGT 1860
TGGCTATAAT CTCTGCATAA CCACATGACT TGGAATGCTT AAATCAGCAA GAAGAATAAT 1920
GGTGGGGTCT TTATACTCAT TCAGGAATGG TTTATCTGAT GCCAGGGCTG TCTTCCTTTC 1980
TCCCCTTTGG ATGGTTGGTG AAATACTTTA ATTGCCCTGT CTGCTCACTT CTAGCTATTT 2040
AAGAGAGAAC CCAGCTTGGT TCTTTTTTGC TCCAAGTGCT TAAAAATAAG TTGGAAAAAG 2100
GAGACGGTGG TGTGGAAATG GCTGAAGAGT TTGCTCTTGT ATCCCTATAG TCCAAGGTTT 2160
CTCAATCTGC ACAATTGACA TTTTTGGCCG GAGTGTTCTT TGTGGTGAGG GCTTTCCTGT 2220
GCATTGTAAG ATGTTCAGCA GTATCCACTC ATGGTCTCTA ACCACTTGAC ACCAGAAACC 2280
CCCCAGCTGT GATAACGCAA AATGTCTCTA GACATCACCA AATGTTCCCT GGGGGTGGCA 2340
AATTTGCCCT TGATTGAGAA CCACCAGTTT AGCTAGTCAA TATGAGGATG GTGGTTTATT 2400
CTCAGAAGAA AAAGATATGT AAGGTCTTTT AGCTCCTTAG AGTGAAGCAA AAGCAAGACT 2460
TCAACCTCAA CCTATCTTTA TGTTTTAAAT ATTAGGGACA ATAAGTTGAA ATAGCTAGAG 2520
GAGCTTCTTT TCAGAACCCC AGATGAGAGC CAATGTCAGA TAAAGTAAGC ATAGCAATGT 2580
AGCAGGAACT ACAATAGAAG ACATTTTCAC TGGAATTACA AAGCAGAATT AAAATTATAT 2640
TGTAGAAGGA AACACCAAGA AAAGAATTTC CAGGGAAAAT CCTCTTTGCA GGTATTAATT 2700
CTTATAATTT TTTGTCTTTT GGATTATCTG TTTACTGTCT CATCTGAACT GATCCCAGGT 2760
GAACGGTTTA TTGCCTAGAT TTGTACTCAG AGGAATTTTT TTTGTTTTGT TTTGTCTTTT 2820
AAGAAAGGAA AGAAAGGATG AAAAAAATAA ACAGAAAACT CAGCTCAGGC ACAATTGTCA 2880
CCAAGGAGTT AAAAGCTTCT TCTTCAATAG AGGAATTGTT CTGGGGGTCC TGGAGACTTA 2940
CCATTGAGCC ATGCAATCTG GGAAGCACAG GAATAAGTAG ACACTTTGAA AATGGATTTG 3000
AATGTTCTCA TCCCTTTTGC AGCTTTTCTT TTTGGCTCTC TCATGTCCTT GGCTTGCTCC 3060
TCTATTCTAC CTCTCTTTCT CCAGCAATAA TATGCAAATG AAGACATGTA TCCATAAGAA 3120
GGAGTGCTCT TCATCAACTA ATAGAGCACC TACCACAGTG TCATACCTGG TAGAGGTGAG 3180
CAATTCATAT TCAAAGGTTG CAAAGTGTTT GTAATATATT CATGAGGCTG GAAGTAAGAA 3240
GAATTAAAAA TTTGTCCTAA TTACAATGAG AACCATTCTA GGTAGTGATC TTGGAGCACA 3300
CATGAATAAC TTTCTGAAGG TGCAACCAAA TCCATTTTTA TTTCTGCCTG GCTTGGTCAC 3360
CTCTGTAAAG GTTTAACTTA GTGTTGTCAA GTAACAGTTA CTGAAAGAGC TGAGAAAAAG 3420
AACAATGAAC AGCAACGATC TTGACTGTGC AACTCAGACA TTCCTGCAGA AAAGACATAT 3480
GTTGCTTTAC AAGAAGGCCA AAGAACTATG GGGCCTTCCC AGCATTTGAC TGTTCATTGC 3540
ATAGAATGAA TTAAATATCC AGTTACTTGA ATGGGTATAA CGCATGAATA TTTGTGTGTC 3600
TGTGTGTGTG TCTGAGTTGT GTGATTTTAT TAGGGGCATC TGCCAATTCT CTCACTGTGG 3660
TTCCTTCTCT GACTTTGCCT GTTCATCATC TAAGGAGGCT AGATCCTTCG CTGACTTCAC 3720
CATTCCTCAA ACCTGTAAGT TTCTCACTTC TTCCAAATTG GCTTTGGCTC TTTCTTCAAC 3780
CTTTCCATTC AAGAGCAATC TTTGCTAAGG AGTAAGTGAA TGTGAAGAGT ACCAACTACA 3840
ACAATTCTAC AGATAATTAG TGGATTGTGT TGTTTGTTGA GAGTGAAGGT TTCTTGGCAT 3900
CTGGTGCCTG ATTAAGGCTT GAGTATTAAG TTCTCAGCAT ATCTCTCTAT TGTCTTGACT 3960
TGAGTTTGCT GCATTTTCTA TGTGCTGTTC GTGACTTGGA GAACTTAAAG TAATCGAGCT 4020
ATGCCAACTT GGGGTGGTAA CAGAGTACTT CCCACCACAG TGTTGAAAGG GAGAGCAAAG 4080
TCTTATGGAT AAACCCTCCT TTCTTTTGGG GACACATGGC TCTCACTTGA GAAGCTCACC 4140
TGTGCTGAAT GTCCACATGG TCACTAAACA TGTTATCCTT AAACCCCCCG TATGCCTGAG 4200
TTGAAAGGGC TCTCTCTTAT TAGGTTTTCA TGGGAACATG AGGCAGCAAA TCTATTGCTA 4260
AGACTTTACC AGGCTCAAAT CATCTGAGGC TGATAGATAT TTGACTTGGT AAGACTTAAG 4320
TAAGGCTCTG GCTCCCAGGG GCATAAGCAA CAGTTTCTTG AATGTGCCAT CTGAGAAGGG 4380
AGACCCAGGT TATGAGTTTT CCTTTGAACA CATTGGTCTT TTCTCAAAGT TCCTGCCTTG 4440
CTAGACTGTT AGCTCTTTGA GGACAGGGAC TATGTCTTAT CAATCACTAT TATTTTCCTG 4500

TTACCTAGCA TGGGACAAGT ACACAACACA TATTTGTTCA ATGAATGAAT GAATGTCTTC 4560
TAAAAGACTC CTCTGATTGG GAGACCATAT CTATAATTGG GATGTGAATC ATTTCTTCAG 4620
TGGAATAAGA GCACAACGGC ACAACCTTCA AGGACATATT ATCTACTATG AACATTTTAC 4680
TGTGAGACTC TTTATTTTGC CTTCTACTTG CGCTGAAATG AAACCAAAAC AGGCCGTTGG 4740
GTTCCACAAG TCAATATATG TTGGATGAGG ATTCTGTTGC CTTATTGGGA ACTGTGAGAC 4800
TTATCTGGTA TGAGAAGCCA GTAATAAACC TTTGACCTGT TTTAACCAAT GAAGATTATG 4860
AATATGTTAA TATGATGTAA ATTGCTATTT AAGTGTAAAG CAGTTCTAAG TTTTAGTATT 4920
TGGGGGATTG GTTTTTATTA TTTTTTTCCT TTTTGAAAAA TACTGAGGGA TCTTTTGATA 4980
AAGTTAGTAA TGCATGTTAG ATTTTAGTTT TGCAAGCATG TTGTTTTTCA AATATATCAA 5040
GTATAGAAAA AGGTAAAACA GTTAAGAAGG AAGGCAATTA TATTATTCTT CTGTAGTTAA 5100
GCAAACACTT GTTGAGTGCC TGCTATGTGC ACGGCATGGG CCCATATGTG TGAGGAGCTT 5160
GTCTAATTAT GTAGGAAGCA ATAGATCTCG GTAGTTACGT ATTGGGCAGA TACTTACTGT 5220
ATGAATGAAA GAACATCACA GTAATCACAA TATCAGAGCT GAATTATCCT CAGTGTAGCT 5280
TCTTGGAATT CAGTTTCTGG AACTAGAGAT AGAGCATTTA TTAAAAAAAA CTCCTGTTGA 5340
GACTGTGTCT TATGAACCTC TGAAACGTAC AAGCCTTCAC AAGTTTAACT AAATTGGGAT 5400
TAATCTTTCT GTAGTTATCT GCATAATTCT TGTTTTTCTT TCCATCTGGC TCCTGGGTTG 5460
ACAATTTGTG GAAACAACTC TATTGCTACT ATTTAAAAAA AATCAGAAAT CTTTCCCTTT 5520
AAGCTATGTT AAATTCAAAC TATTCCTGCT ATTCCTGTTT TGTCAAAGAA TTATATTTTT 5580
CAAAATATGT TTATTTGTTT GATGGGTCCC AGGAAACACT AATAAAAACC ACAGAGACCA 5640
GCCTGGAAAA AAAAAAAAAA AAAAAAA 5667

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 300 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ile Leu Glu Gly Gly Gly Val Met Asn Leu Asn Pro Gly Asn Asn
1   5   10   15
Leu Leu His Gln Pro Pro Ala Trp Thr Asp Ser Tyr Ser Thr Cys Asn
            20   25   30
Val Ser Ser Gly Phe Phe Gly Gly Gln Trp His Glu Ile His Pro Gln
        35   40   45
Tyr Trp Thr Lys Tyr Gln Val Trp Glu Trp Leu Gln His Leu Leu Asp
    50   55   60
Thr Asn Gln Leu Asp Ala Asn Cys Ile Pro Phe Gln Glu Phe Asp Ile
65   70   75   80
Asn Gly Glu His Leu Cys Ser Met Ser Leu Gln Glu Phe Thr Arg Ala
                85   90   95
Ala Gly Thr Ala Gly Gln Leu Leu Tyr Ser Asn Leu Gln His Leu Lys
            100   105   110
Trp Asn Gly Gln Cys Ser Ser Asp Leu Phe Gln Ser Thr His Asn Val
        115   120   125
Ile Val Lys Thr Glu Gln Thr Glu Pro Ser Ile Met Asn Thr Trp Lys
    130   135   140
Asp Glu Asn Tyr Leu Tyr Asp Thr Asn Tyr Gly Ser Thr Val Asp Leu
145   150   155   160
Leu Asp Ser Lys Thr Phe Cys Arg Ala Gln Ile Ser Met Thr Thr Thr
                165   170   175
Ser His Leu Pro Val Ala Glu Ser Pro Asp Met Lys Lys Glu Gln Asp

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            180                      185                      190
Pro Pro Ala Lys Cys His Thr Lys Lys His Asn Pro Arg Gly Thr His
        195                      200                      205
Leu Trp Glu Phe Ile Arg Asp Ile Leu Leu Asn Pro Asp Lys Asn Pro
    210                      215                      220
Gly Leu Ile Lys Trp Glu Asp Arg Ser Glu Gly Val Phe Arg Phe Leu
225                      230                      235                      240
Lys Ser Glu Ala Val Ala Gln Leu Trp Gly Lys Lys Lys Asn Asn Ser
                245                      250                      255
Ser Met Thr Tyr Glu Lys Leu Ser Arg Ala Met Arg Tyr Tyr Tyr Lys
            260                      265                      270
Arg Glu Ile Leu Glu Arg Val Asp Gly Arg Arg Leu Val Tyr Lys Phe
        275                      280                      285
Gly Lys Asn Ala Arg Gly Trp Arg Glu Asn Glu Asn
    290                      295                      300
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2428 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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CAGGGGTGCC GGGTTGCTCA GGCCATGGGA GCCACACCTG TTATTGCTGC CTCTGATTTG     60
TGTGACACTG AGAAGCCCAC AGGCCTGTCC CTCCAACTCG GTGGACCCTC TCTGTGTGCA    120
TTTGGTGTGT GAGCCAGCTC TGAGAAGGGT TCAGAAGCCA CTGGAGGCAT CTGGGGACCT    180
CAGCTTCCAT GCCATCTCTG CCTCACTCCC ACAGGGTAAT GTTGGACTCG GTGACACACA    240
GCACCTTCCT GCCTAATGCA TCCTTCTGCG ATCCCCTGAT GTCGTGGACT GATCTGTTCA    300
GCAATGAAGA GTACTACCCT GCCTTTGAGC ATCAGACAGC CTGTGACTCA TACTGGACAT    360
CAGTCCACCC TGAATACTGG ACTAAGCGCC ATGTGTGGGA GTGGCTCCAG TTCTGCTGCG    420
ACCAGTACAA GTTGGACACC AATTGCATCT CCTTCTGCAA CTTCAACATC AGTGGCCTGC    480
AGCTGTGCAG CATGACACAG GAGGAGTTCG TCGAGGCAGC TGGCCTCTGC GGCGAGTACC    540
TGTACTTCAT CCTCCAGAAC ATCCGCACAC AAGGTTACTC CTTTTTTAAT GACGCTGAAG    600
AAAGCAAGGC CACCATCAAA GACTATGCTG ATTCCAACTG CTTGAAAACA AGTGGCATCA    660
AAAGTCAAGA CTGTCACAGT CATAGTAGAA CAAGCCTCCA AAGTTCTCAT CTATGGGAAT    720
TTGTACGAGA CCTGCTTCTA TCTCCTGAAG AAAACTGTGG CATTCTGGAA TGGGAAGATA    780
GGGAACAAGG AATTTTTCGG GTGGTTAAAT CGGAAGCCCT GGCAAAGATG TGGGGACAAA    840
GGAAGAAAAA TGACAGAATG ACGTATGAAA AGTTGAGCAG AGCCCTGAGA TACTACTATA    900
AAACAGGAAT TTTGGAGCGG GTTGACCGAA GGTTAGTGTA CAAATTTGGA AAAAATGCAC    960
ACGGGTGGCA GGAAGACAAG CTATGATCTG CTCCAGGCAT CAAGCTCATT TTATGGATTT   1020
CTGTCTTTTA AAACAATCAG ATTGCAATAG ACATTCGAAA GGCTTCATTT TCTTCTCTTT   1080
TTTTTTAACC TGCAAACATG CTGATAAAAT TTCTCCACAT CTCAGCTTAC ATTTGGATTC   1140
AGAGTTGTTG TCTACGGAGG GTGAGAGCAG AAACTCTTAA GAAATCCTTT CTTCTCCCTA   1200
AGGGGATGAG GGGATGATCT TTTGTGGTGT CTTGATCAAA CTTTATTTTC CTAGAGTTGT   1260
GGAATGACAA CAGCCCATGC CATTGATGCT GATCAGAGAA AAACTATTCA ATTCTGCCAT   1320
TAGAGACACA TCCAATGCTC CCATCCCAAA GGTTCAAAAG TTTTCAAATA ACTGTGGCAG   1380
CTCACCAAAG GTGGGGGAAA GCATGATTAG TTTGCAGGTT ATGGTAGGAG AGGGTGAGAT   1440
ATAAGACATA CATACTTTAG ATTTTAAATT ATTAAAGTCA AAAATCCATA GAAAAGTATC   1500
CCTTTTTTTT TTTTTTGAGA CGGGTTCTCA CTATGTTGCC CAGGGCTGGT CTTGAACTCC   1560
TATGCTCAAG TGATCCTCCC ACCTCGGCCT CCCAAAGTAC TGTGATTACA AGCGTGAGCC   1620
ACGGCACCTG GGCAGAAAAG TATCTTAATT AATGAAAGAG CTAAGCCATC AAGCTGGGAC   1680
```

TTAATTGGAT TTAACATAGG TTCACAGAAA GTTTCCTAAC CAGAGCATCT TTTTGACCAC 1740
TCAGCAAAAC TTCCACAGAC ATCCTTCTGG ACTTAAACAC TTAACATTAA CCACATTATT 1800
AATTGTTGCT GAGTTTATTC CCCCTTCTAA CTGATGGCTG GCATCTGATA TGCAGAGTTA 1860
GTCAACAGAC ACTGGCATCA ATTACAAAAT CACTGCTGTT TCTGTGATTC AAGCTGTCAA 1920
CACAATAAAA TCGAAATTCA TTGATTCCAT CTCTGGTCCA GATGTTAAAC GTTTATAAAA 1980
CCGGAAATGT CCTAACAACT CTGTAATGGC AAATTAAATT GTGTGTCTTT TTTGTTTTGT 2040
CTTTCTACCT GATGTGTATT CAAGCGCTAT AACACGTATT TCCTTGACAA AAATAGTGAC 2100
AGTGAATTCA CACTAATAAA TGTTCATAGG TTAAAGTCTG CACTGACATT TTCTCATCAA 2160
TCACTGGTAT GTAAGTTATC AGTGACTGAC AGCTAGGTGG ACTGCCCCTA GGACTTCTGT 2220
TTCACCAGAG CAGGAATCAA GTGGTGAGGC ACTGAATCGC TGTACAGGCT GAAGACCTCC 2280
TTATTAGAGT TGAACTTCAA AGTAACTTGT TTTAAAAAAT GTGAATTACT GTAAAATAAT 2340
CTATTTTGGA TTCATGTGTT TTCCAGGTGG ATATAGTTTG TAAACAATGT GAATAAAGTA 2400
TTTAACATGT TCAAAAAAAA AAAAAAAA 2428

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 265 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Pro Ser Leu Pro His Ser His Arg Val Met Leu Asp Ser Val Thr
1 5 10 15
His Ser Thr Phe Leu Pro Asn Ala Ser Phe Cys Asp Pro Leu Met Ser
20 25 30
Trp Thr Asp Leu Phe Ser Asn Glu Glu Tyr Tyr Pro Ala Phe Glu His
35 40 45
Gln Thr Ala Cys Asp Ser Tyr Trp Thr Ser Val His Pro Glu Tyr Trp
50 55 60
Thr Lys Arg His Val Trp Glu Trp Leu Gln Phe Cys Cys Asp Gln Tyr
65 70 75 80
Lys Leu Asp Thr Asn Cys Ile Ser Phe Cys Asn Phe Asn Ile Ser Gly
85 90 95
Leu Gln Leu Cys Ser Met Thr Gln Glu Glu Phe Val Glu Ala Ala Gly
100 105 110
Leu Cys Gly Glu Tyr Leu Tyr Phe Ile Leu Gln Asn Ile Arg Thr Gln
115 120 125
Gly Tyr Ser Phe Phe Asn Asp Ala Glu Glu Ser Lys Ala Thr Ile Lys
130 135 140
Asp Tyr Ala Asp Ser Asn Cys Leu Lys Thr Ser Gly Ile Lys Ser Gln
145 150 155 160
Asp Cys His Ser His Ser Arg Thr Ser Leu Gln Ser Ser His Leu Trp
165 170 175
Glu Phe Val Arg Asp Leu Leu Leu Ser Pro Glu Glu Asn Cys Gly Ile
180 185 190
Leu Glu Trp Glu Asp Arg Glu Gln Gly Ile Phe Arg Val Val Lys Ser
195 200 205
Glu Ala Leu Ala Lys Met Trp Gly Gln Arg Lys Lys Asn Asp Arg Met
210 215 220
Thr Tyr Glu Lys Leu Ser Arg Ala Leu Arg Tyr Tyr Tyr Lys Thr Gly
225 230 235 240

```
Ile Leu Glu Arg Val Asp Arg Arg Leu Val Tyr Lys Phe Gly-Lys Asn
                245                 250                 255
Ala His Gly Trp Gln Glu Asp Lys Leu
            260                 265
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2280 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

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CTGGGAGCGC CTGCCTTCTC TTGCCTTGAA AGCCTCCTCT TTGGACCTAG CCACCGCTGC     60
CCTCACGGTA ATGTTGGACT CGGTGACACA CAGCACCTTC CTGCCTAATG CATCCTTCTG    120
CGATCCCCTG ATGTCGTGGA CTGATCTGTT CAGCAATGAA GAGTACTACC CTGCCTTTGA    180
GCATCAGACA GCCTGTGACT CATACTGGAC ATCAGTCCAC CCTGAATACT GGACTAAGCG    240
CCATGTGTGG GAGTGGCTCC AGTTCTGCTG CGACCAGTAC AAGTTGGACA CCAATTGCAT    300
CTCCTTCTGC AACTTCAACA TCAGTGGCCT GCAGCTGTGC AGCATGACAC AGGAGGAGTT    360
CGTCGAGGCA GCTGGCCTCT GCGGCGAGTA CCTGTACTTC ATCCTCCAGA ACATCCGCAC    420
ACAAGGTTAC TCCTTTTTTA ATGACGCTGA AGAAAGCAAG GCCACCATCA AAGACTATGC    480
TGATTCCAAC TGCTTGAAAA CAAGTGGCAT CAAAAGTCAA GACTGTCACA GTCATAGTAG    540
AACAAGCCTC CAAAGTTCTC ATCTATGGGA ATTTGTACGA GACCTGCTTC TATCTCCTGA    600
AGAAAACTGT GGCATTCTGG AATGGGAAGA TAGGGAACAA GGAATTTTTC GGGTGGTTAA    660
ATCGGAAGCC CTGGCAAAGA TGTGGGGACA AAGGAAGAAA AATGACAGAA TGACGTATGA    720
AAAGTTGAGC AGAGCCCTGA GATACTACTA TAAAACAGGA ATTTTGGAGC GGGTTGACCG    780
AAGGTTAGTG TACAAATTTG GAAAAAATGC ACACGGGTGG CAGGAAGACA AGCTATGATC    840
TGCTCCAGGC ATCAAGCTCA TTTTATGGAT TTCTGTCTTT TAAAACAATC AGATTGCAAT    900
AGACATTCGA AAGGCTTCAT TTTCTTCTCT TTTTTTTTAA CCTGCAAACA TGCTGATAAA    960
ATTTCTCCAC ATCTCAGCTT ACATTTGGAT TCAGAGTTGT TGTCTACGGA GGGTGAGAGC   1020
AGAAACTCTT AAGAAATCCT TTCTTCTCCC TAAGGGGATG AGGGGATGAT CTTTTGTGGT   1080
GTCTTGATCA AACTTTATTT TCCTAGAGTT GTGGAATGAC AACAGCCCAT GCCATTGATG   1140
CTGATCAGAG AAAAACTATT CAATTCTGCC ATTAGAGACA CATCCAATGC TCCCATCCCA   1200
AAGGTTCAAA AGTTTTCAAA TAACTGTGGC AGCTCACCAA AGGTGGGGGA AAGCATGATT   1260
AGTTTGCAGG TTATGGTAGG AGAGGGTGAG ATATAAGACA TACATACTTT AGATTTTAAA   1320
TTATTAAAGT CAAAAATCCA TAGAAAAGTA TCCCTTTTTT TTTTTTTTGA GACGGGTTCT   1380
CACTATGTTG CCCAGGGCTG GTCTTGAACT CCTATGCTCA AGTGATCCTC CCACCTCGGC   1440
CTCCCAAAGT ACTGTGATTA CAAGCGTGAG CCACGGCACC TGGGCAGAAA AGTATCTTAA   1500
TTAATGAAAG AGCTAAGCCA TCAAGCTGGG ACTTAATTGG ATTTAACATA GGTTCACAGA   1560
AAGTTTCCTA ACCAGAGCAT CTTTTTGACC ACTCAGCAAA ACTTCCACAG ACATCCTTCT   1620
GGACTTAAAC ACTTAACATT AACCACATTA TTAATTGTTG CTGAGTTTAT TCCCCCTTCT   1680
AACTGATGGC TGGCATCTGA TATGCAGAGT TAGTCAACAG ACACTGGCAT CAATTACAAA   1740
ATCACTGCTG TTTCTGTGAT TCAAGCTGTC AACACAATAA AATCGAAATT CATTGATTCC   1800
ATCTCTGGTC CAGATGTTAA ACGTTTATAA AACCGGAAAT GTCCTAACAA CTCTGTAATG   1860
GCAAATTAAA TTGTGTGTCT TTTTTGTTTT GTCTTTCTAC CTGATGTGTA TTCAAGCGCT   1920
ATAACACGTA TTTCCTTGAC AAAAATAGTG ACAGTGAATT CACACTAATA AATGTTCATA   1980
GGTTAAAGTC TGCACTGACA TTTTCTCATC AATCACTGGT ATGTAAGTTA TCAGTGACTG   2040
ACAGCTAGGT GGACTGCCCC TAGGACTTCT GTTTCACCAG AGCAGGAATC AAGTGGTGAG   2100
GCACTGAATC GCTGTACAGG CTGAAGACCT CCTTATTAGA GTTGAACTTC AAAGTAACTT   2160
GTTTTAAAAA ATGTGAATTA CTGTAAAATA ATCTATTTTG GATTCATGTG TTTTCCAGGT   2220
GGATATAGTT TGTAAACAAT GTGAATAAAG TATTTAACAT GTTCAAAAAA AAAAAAAAAA   2280
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 255 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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Met Leu Asp Ser Val Thr His Ser Thr Phe Leu Pro Asn Ala Ser Phe
 1               5                  10                  15
Cys Asp Pro Leu Met Ser Trp Thr Asp Leu Phe Ser Asn Glu Glu Tyr
            20                  25                  30
Tyr Pro Ala Phe Glu His Gln Thr Ala Cys Asp Ser Tyr Trp Thr Ser
        35                  40                  45
Val His Pro Glu Tyr Trp Thr Lys Arg His Val Trp Glu Trp Leu Gln
    50                  55                  60
Phe Cys Cys Asp Gln Tyr Lys Leu Asp Thr Asn Cys Ile Ser Phe Cys
65                  70                  75                  80
Asn Phe Asn Ile Ser Gly Leu Gln Leu Cys Ser Met Thr Gln Glu Glu
                85                  90                  95
Phe Val Glu Ala Ala Gly Leu Cys Gly Glu Tyr Leu Tyr Phe Ile Leu
            100                 105                 110
Gln Asn Ile Arg Thr Gln Gly Tyr Ser Phe Phe Asn Asp Ala Glu Glu
        115                 120                 125
Ser Lys Ala Thr Ile Lys Asp Tyr Ala Asp Ser Asn Cys Leu Lys Thr
    130                 135                 140
Ser Gly Ile Lys Ser Gln Asp Cys His Ser His Ser Arg Thr Ser Leu
145                 150                 155                 160
Gln Ser Ser His Leu Trp Glu Phe Val Arg Asp Leu Leu Leu Ser Pro
                165                 170                 175
Glu Glu Asn Cys Gly Ile Leu Glu Trp Glu Asp Arg Glu Gln Gly Ile
            180                 185                 190
Phe Arg Val Val Lys Ser Glu Ala Leu Ala Lys Met Trp Gly Gln Arg
        195                 200                 205
Lys Lys Asn Asp Arg Met Thr Tyr Glu Lys Leu Ser Arg Ala Leu Arg
    210                 215                 220
Tyr Tyr Tyr Lys Thr Gly Ile Leu Glu Arg Val Asp Arg Arg Leu Val
225                 230                 235                 240
Tyr Lys Phe Gly Lys Asn Ala His Gly Trp Gln Glu Asp Lys Leu
                245                 250                 255
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2498 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
GAGGGGCTGA CAGCGGCGTC CCTCGTCTGG GCAGCCTCCG CTCTGCCACT CTCCTCCCGT     60
CCTGAGGATG GGACCCCCGG AAAAGCGGCC TCTGGAGGCC TGCCATGGCA CCCAGAGCAG    120
CCATTTTCCT CCCAGTTCTG GGGCTTTGGA AGGAGCTTGC GGATGAGGAG AGGGAGCCTC    180
CGCAGGGCTC TGGCTCCCCT CCAGGGGCCG AGGCCGCACA CAAAGCCGCT CTGTGGCCCA    240
ATTACACCTA CTGGATAGGA TTGTTGAGGG GACCTGAGAA ACTTGAGACG ACAAGAACGC    300
GTAGCGCCTC GGCTGGCTGA GGGTGCTGAG CCCTCGTGTT GTGTTCTCTC CAGCTTTCCC    360
CGTGCCTCAG CCACTCTTCA CGTTCCATCT GTGCTCTGTG CTGACCCGCC TGTGACTCAT    420
ACTGGACATC AGTCCACCCT GAATACTGGA CTAAGCGCCA TGTGTGGGAG TGGCTCCAGT    480
TCTGCTGCGA CCAGTACAAG TTGGACACCA ATTGCATCTC CTTCTGCAAC TTCAACATCA    540
GTGGCCTGCA GCTGTGCAGC ATGACACAGG AGGAGTTCGT CGAGGCAGCT GGCCTCTGCG    600
GCGAGTACCT GTACTTCATC CTCCAGAACA TCCGCACACA AGGTTACTCC TTTTTTAATG    660
ACGCTGAAGA AAGCAAGGCC ACCATCAAAG ACTATGCTGA TTCCAACTGC TTGAAAAACA    720
GTGGCATCAA AAGTCAAGAC TGTCACAGTC ATAGTAGAAC AAGCCTCCAA AGTTCTCATC    780
TATGGGAATT TGTACGAGAC CTGCTTCTAT CTCCTGAAGA AAACTGTGGC ATTCTGGAAT    840
GGGAAGATAG GGAACAAGGA ATTTTTCGGG TGGTTAAATC GGAAGCCCTG GCAAAGATGT    900
GGGGACAAAG GAAGAAAAAT GACAGAATGA CGTATGAAAA GTTGAGCAGA GCCCTGAGAT    960
ACTACTATAA AACAGGAATT TTGGAGCGGG TTGACCGAAG GTTAGTGTAC AAATTTGGAA   1020
AAAATGCACA CGGGTGGCAG GAAGACAAGC TATGATCTGC TCCAGGCATC AAGCTCATTT   1080
TATGGATTTC TGTCTTTTAA AACAATCAGA TTGCAATAGA CATTCGAAAG GCTTCATTTT   1140
CTTCTCTTTT TTTTTAACCT GCAAACATGC TGATAAAATT TCTCCACATC TCAGCTTACA   1200
TTTGGATTCA GAGTTGTTGT CTACGGAGGG TGAGAGCAGA AACTCTTAAG AAATCCTTTC   1260
TTCTCCCTAA GGGGATGAGG GGATGATCTT TTGTGGTGTC TTGATCAAAC TTTATTTTCC   1320
TAGAGTTGTG GAATGACAAC AGCCCATGCC ATTGATGCTG ATCAGAGAAA AACTATTCAA   1380
TTCTGCCATT AGAGACACAT CCAATGCTCC CATCCCAAAG GTTCAAAAGT TTTCAAATAA   1440
CTGTGGCAGC TCACCAAAGG TGGGGGAAAG CATGATTAGT TTGCAGGTTA TGGTAGGAGA   1500
GGGTGAGATA TAAGACATAC ATACTTTAGA TTTTAAATTA TTAAAGTCAA AAATCCATAG   1560
AAAAGTATCC CTTTTTTTTT TTTTTGAGAC GGGTTCTCAC TATGTTGCCC AGGGCTGGTC   1620
TTGAACTCCT ATGCTCAAGT GATCCTCCCA CCTCGGCCTC CCAAAGTACT GTGATTACAA   1680
GCGTGAGCCA CGGCACCTGG GCAGAAAAGT ATCTTAATTA ATGAAAGAGC TAAGCCATCA   1740
AGCTGGGACT TAATTGGATT TAACATAGGT TCACAGAAAG TTTCCTAACC AGAGCATCTT   1800
TTTGACCACT CAGCAAAACT TCCACAGACA TCCTTCTGGA CTTAAACACT TAACATTAAC   1860
CACATTATTA ATTGTTGCTG AGTTTATTCC CCCTTCTAAC TGATGGCTGG CATCTGATAT   1920
GCAGAGTTAG TCAACAGACA CTGGCATCAA TTACAAAATC ACTGCTGTTT CTGTGATTCA   1980
AGCTGTCAAC ACAATAAAAT CGAAATTCAT TGATTCCATC TCTGGTCCCA GATGTTAAAC   2040
GTTTATAAAA CCGGAAATGT CCTAACAACT CTGTAATGGC AAATTAAATT GTGTGTCTTT   2100
TTTGTTTTGT CTTTCTACCT GATGTGTATT CAAGCGCTAT AACACGTATT TCCTTGACAA   2160
AAATAGTGAC AGTGAATTCA CACTAATAAA TGTTCATAGG TTAAAGTCTG CACTGACATT   2220
TTCTCATCAA TCACTGGTAT GTAAGTTATC AGTGACTGAC AGCTAGGTGG ACTGCCCCTA   2280
GGACTTCTGT TTCACCAGAG CAGGAATCAA GTGGTGAGGC ACTGAATCGC TGTACAGGCT   2340
GAAGACCTCC TTATTAGAGT TGAACTTCAA AGTAACTTGT TTTAAAAAAT GTGAATTACT   2400
GTAAAATAAT CTATTTTGGA TTCATGTGTT TTCCAGGTGG ATATAGTTTG TAAACAATGT   2460
GAATAAAGTA TTTAACATGT TCAAAAAAAA AAAAAAAA                            2498
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 164 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Thr Gln Glu Glu Phe Val Glu Ala Ala Gly Leu Cys Gly Glu Tyr

```
 1               5                   10                  15
Leu Tyr Phe Ile Leu Gln Asn Ile Arg Thr Gln Gly Tyr Ser Phe Phe
            20                  25                  30
Asn Asp Ala Glu Glu Ser Lys Ala Thr Ile Lys Asp Tyr Ala Asp Ser
        35                  40                  45
Asn Cys Leu Lys Thr Ser Gly Ile Lys Ser Gln Asp Cys His Ser His
    50                  55                  60
Ser Arg Thr Ser Leu Gln Ser Ser His Leu Trp Glu Phe Val Arg Asp
65                  70                  75                  80
Leu Leu Leu Ser Pro Glu Glu Asn Cys Gly Ile Leu Glu Trp Glu Asp
                85                  90                  95
Arg Glu Gln Gly Ile Phe Arg Val Val Lys Ser Glu Ala Leu Ala Lys
            100                 105                 110
Met Trp Gly Gln Arg Lys Lys Asn Asp Arg Met Thr Tyr Glu Lys Leu
        115                 120                 125
Ser Arg Ala Leu Arg Tyr Tyr Tyr Lys Thr Gly Ile Leu Glu Arg Val
    130                 135                 140
Asp Arg Arg Leu Val Tyr Lys Phe Gly Lys Asn Ala His Gly Trp Gln
145                 150                 155                 160
Glu Asp Lys Leu
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AAATGAGCCA ATGTTTGTAA T 21

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

AAATGAGCCA GTGTTTGTAA T 21

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 736 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
AGGAAGTGAA GAACCTAGAT AATCCACCAA CCGGATAATC AGCTCTTGCA TATTTGAGAG    60
TTGACTGCTT GACCTAAGCA TCTCCTCATA AGGTACCCTC CCTCCCAGGA CCTTCCCTTT   120
CAAACCTCTC AAGGCTCTTA CCTGGGGCCA GGGGAGATAG GCTTTTCAAA GTCCATTGAA   180
TTGCCAAGAG TCTCTGTCAA GAAGGCAGTC ATGGTGCCTG GAGAGGGAAC TTGCTGGGAG   240
CCCCTTCAGA GCCTGGTACT TATAGAGCTA GGGAAAAGAT CTTGATGCCA AAGCAGGGTG   300
GACTAAATAC AGACTAATAA ATGAGACAGG TGCTCAAGAG GGCCCCTCCA TACCATCATC   360
TCCTCCAGAT TTGGACTTCT ACTCACTTTG CTTTTACATT CCCTCTTCCC GATGGTGTCT   420
TTGGTGAGCA GGGTGCTTTT CACCTGAAAC AGCCTCTGAG CTGAAAAGAA CAGTCACCAC   480
CAAATCAATT CCTCATCCAT TAACAGGTTG TCTCTCTGTT CTTGAGACAC AGGCATTACC   540
TGGTTAGACC TGTTTTGTTT GAACACTAAC GTGTGAGTTG GCCAAATGCA AATGAGCCAA   600
TGTTTGTAAT CCTTTATTTT ATTTTTTTAA AGGGCTGGGT AGCCAATCAG AAGAGGGGGA   660
AGTGACTTAG GGAATTCCCG GTTGGTGGCT TATTGCTTAA CATCCTACAA AATGATTTAA   720
AATTATTGTT ATATGC                                                   736
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 333 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
GCCAGAGTCC TCCTTGAGAA CTTACAATGT GTCCATATTA AGGATCTGCT GTGTTTGATG    60
ATTTTGTGAT TACACTTTAA ACTTCTTATC CATAAAGGAC ATACTTGATA TATCTGAGAC   120
TTGTAGTAGA AGGCCTTGAG ACATCCATCT CATCCCATCA TTATCTATCT ATCATCTATC   180
TATCTATCTA TCTATCTATC TATCTATCTA TCTATCATCT ATCTATCTAT CGCCAGTACT   240
GTCTTGTTGA AGTTGGCAGT AGGGTGAAAG ACCTCAAACT CCAAAGGACT TTCCGTATGG   300
ATGCAATATA CCTGCAATTC TAGCTTTTCT GTG                                333
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
ACAGAATGAC RTATGAAAAG T                                              21
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTAACCAAGC KCAAGCCACC C 21

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAGGAGCCCA YCTGAGTGCA G 21

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CGTTCCATCT STGCTCTGTG C 21

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGCGCCTCGG YTGGCTGAGG G 21

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TGTATTCAAG YGCTATAACA C 21

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CACTGAGAAG CCNACAGGCC TGT 23

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CCCACAGGCC WGTCCCTCCA A 21

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CGTCCATCTC YAGCTCCAGG G 21

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GACTTGATAA YGCCCGTGGT G 21

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ACTTGATAAC RCCCGTGGTG C 21

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CTCCCCTCCA WGAGCCACAG C 21

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

ATTTCCTGCA TNGTCTGGAC TT 22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ATCCAAACAC YTGAGTGGAA A 21

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AGTTTCCTCA RTGCGGGAGC T 21

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GCGAGCACCT YTGCAGCATG A 21

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TTCACCCGGG YGGCAGGGAC G 21

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGGGGAAAA NNGATCGCTG AC 22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GTCAATTAAA YGGCTCTCAT T 21

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TAGATCATTC RTAACCTGCC T 21

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

AAAGAGAAAT WCTGGAGCGT G 21

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ATGAGGGGAA MAAGAAACTA C 21

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TTTTGTATGT KACATGATTT A 21

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AGCTTGGTTC YTTTTTGCTC C 21

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

TTGACACCAG RAACCCCCCA G 21

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

AAATGAGCCA RTGTTTGTAA T 21

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

ATCCATTTTG YATTCCTCAT T 21

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTGGAGCTCA RACCAGACAG C 21

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GCCAGTGCAG SCATCATTAC C 21

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

AGTTCAAATC RTAATTTTTA T 21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TCATCAGAAT YTAAATCTCC C 21

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GGAGATTCAG NTGAAGCAAG A 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

TTTTTCCACA YCCAGCCTGG C 21

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CCCAGCCTGG YGAACCCTGG C 21

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CTCTTCATCA YGGTCAAATA C 21

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CAACTTGCTG YCAAAGTGCT G 21

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

TACTATGTGC YAGATACTAA G 21

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ATGCCACTTT RRGACAACTT GAG 23

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CGCATGCCTG KAAAGAAGAG A 21

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GGATAAGCAC MAGTGAGCCT G 21

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

AAAGCCAGAC RGCAACTTGT G 21

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

TCTCAAAAAG RGTGATAGGA G 21

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TCTGAATCCT STCTCCTCCT T 21

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TAGAACCAGG WTGTGGGACC A 21

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

TTCTTGTGTC RGGCGCAAAA C 21

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

AACCAACATG RAGAAACCCC A 21

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

AATAAACTAT RGTTCACCTA G 21

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

ACATATTTGT RTCTCATATG A 21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

CAAAGCAGTT YCTAATAATC C 21

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

AGATCCTAAC YGGGGCCTCC T 21

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTCTTTCTCT YTGCTTCCTC C 21

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

TTAGGAATCC WCAAATATGT A 21

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GTCTGACTCC RCCTCCCTCA T 21

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

GAATCACATC RTGAGAAATG T 21

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

AATTCAATCC YTCACAGACT T 21

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GTGTAGCCAG RGTTGCTAAT T 21

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

CCTAGAAATA SCCAAGGGCA C 21

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

AAATTCTCAT RCCTCACCCT C 21

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

TCCCACCCCT RTCACCTTCA T 21

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CCTCATTCTC RGAAGCCAAC A 21

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GAAGAGCCGT YCAGTCCCTT T 21

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

TCCATAGGCT YTTTATTTGG C 21

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

TCGTTTAGTA YACAGGCTTT G 21

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GCCTCAGTTG YCCCAGCTAT A 21

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

AGCAAAATGC WCTATGCACT G 21

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GTGTCCTGAC NNNNNNNNNN NACACTGCCT G 31

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

ATCAGATAAC RCCTACACTT A 21

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

TCTCTCTTCT SCCTGCCCTG T 21

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

TGGACACAGG KAGGGGAATA T 21

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

TGTCACTTGC RCATACAAGG C 21

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

ATCATCAGAT YAGCCCAGAA T 21

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

TCAACAGAGA RAGTTAATGG T 21

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

AGCAATAATG YTTCCCTTTT C 21

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

TCTAGCTTTT YTGTGTTTTT T 21

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

GATTCCTTAA YGCTTGATAC T 21

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CCTCCTCCAG YACCAAAGTG G 21

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

ATGGCCACAG RTCAAATCCT G 21

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

ACTGAGTGTT YATGCCAATT T 21

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

GACAAGCCCT RTCTGACACA C 21

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

TGAAAAGCCT YCTTGCTGCC T 21

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

TCCTGGAGTT YCTTTGCTCC C 21

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

GATTCCAAAT WAACTAAAGA T 21

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GACCTCAAGT CRTCCACCCG CC 22

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

AACAAATACT MCCCCGCAAC CC 22

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

ATTTTTTTTT NAAGGAAAAT A 21

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

AAATTTCCCC MAAACAAGCA G 21

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

GAGAAAGGGT RTGTGTGTGT G 21

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GTGTGTGTGT NNNNGTATGT GCGCGTG 27

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

ATCGGGAACC YCATACCCCA A 21

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

TTTGTTTCGC MATGAGGTAC G 21

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

TGAGGGTGTT STGGGCTGGA C 21

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

TCTTCATTGG YATCTGAATG T 21

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

GCGAGCACCT YTGCAGCATG A 21

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

AACCCCCCCC MCACACACAC A 21

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TCAGTGCTCT STAATCAGTC A 21

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

TCTTTGTGAA ANNAATTAGT CTG 23

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

GCTGCCCTGA SAGCTGGGCC A 21

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CCTTCTGATC YTTGTTTGCT G 21

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

GGAACACTGA KTCTTGATTA G 21

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

TAGGCTTCTC YTGATAATTG A 21

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

TCTTAAAATA MTTGGCTTGT A 21

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

TAGATCATTA RTAACCTGCC T 21

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

ATGAGGGGAA MAAGAAACTA C 21

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

TTGACACCAG RAACCCCCCA G 21

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

TGTTTTAAAT RTTAGGGACA A 21

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

GTAAGCATAG YAATGTAGCA G 21

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

GGCTCTTTCT KCAACCTTTC C 21

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

GACCCAGGTT RTGAGTTTTC C 21

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

GACAGAATGA YATATGAAAA G 21

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

TGTGTGACAC YGAGAAGCCC A 21

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

AGTACTGGAC MAAGTACCAG G 21

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

CCTGGGAGCA RGTATTGCAT T 21

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

AGATTTGAGG YCTCAGGTCC C 21

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

TGTCAATGTC RCATGATAAG C 21

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

TTGCCCCAGT KTTCTCCGGG C 21

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

TATGAGCAGC RTAGGGAGTG G 21

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

AGTTGACTGA AAAANTAAAT AAGAC 25

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

ATTCAAATAG SCTCTAGAAA C 21

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

CCCAGAATTT MATATCCATT C 21

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

TGACCCAACA RAAACTCACT G 21

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

CCAGAATATA WCATCAGCCC T 21

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

CATCAGCCCT WCTGAGGAGA T 21

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

CCAGAACAGA YTTTATTCTG T 21

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

TTCAGCCATC YTTCCAGTTG T 21

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

TCACTAACTC WAAAACGACA T 21

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

AACTCAAAAA YGACATCCTC C 21

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

GAACTGCACA RGTTGCACAC T 21

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

TTGTTCCATG SACTACCTCC T 21

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

ACAGCAGGCA YTCAACAAAT T 21

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

TTATTTTTGG STTTGTTTTA A 21

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

TAGGCTGTTC YCTGCCATCA C 21

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

GTGCTCTGGG MCACACAGCT C 21

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

AGACCCGATA RGAGCTCCTT C 21

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

CATCTTGCGC RGTCATGTAA G 21

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

CAGCACAGCT RTTCCCTCAA A 21

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

TTTGGAAACA YGGTGAAGTA T 21

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

ACACGGTGAA RTATTGTCTC C 21

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

AAAAGTGGAT MCTCTGCAAA C 21

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

CTTCAAATGC RGCTATTAAA G 21

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

CCTGGGAGCA YGGTAAATCA G 21

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

TGAAAATGTC RCTTTCTCAC CT 22

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

CCTGATATTT RCCAACAAGA A 21

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

AAAGGGTTAG YTTGTCCCCT T 21

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

TGAAAATAAA ASACAATTTT TT 22

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

CTGCTGTGGA CGAATAGG 18

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

TCAATATAAT CTTGCTTAAC TTGG 24

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

GACCTGTTTG GGTTGATTTC AG 22

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

GTTTCTTACA GTGTCTTGCT ATCACATCAC C 31

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

GAGGACTGGC AGTACCAAGT AAAC 24

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

GTTTCTTTGG TTCATTCTAA GATGGCTGG 29

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

GCTGAGGCAG GAGAAAAGAC AAG 23

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

GTTTCTTCAT GCAAAGGTCA GGAGGTAGG 29

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

GTTGCTTCCA GACGAGGTAC ATG 23

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

GTTTCTTCAA TGGCTCCACA AACATCTCTG 30

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

AGGTTTAGGG GACAGGGTTT GG 22

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

GTTTCTTTCC TGGCTAACAC GGTGAAATC 29

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

GTTTCTTATT GCCTCCTCCC AAAATTC 27

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

AGAGGCCACT GGAAGACGAA 20

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

AACTGGAGTC AGGCAAAACG TG 22

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

GTTTCTTTGG CTGGTAAGGA AAGAAACCAC 30

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

GGCTAGGTTC ATAAACTCTG TGCTG 25

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

GTTTCTTGAT TGTTTGAGAT CCTTGACCCA G 31

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

GCCGAAATCA CAACACTGCA TC 22

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

GTTTCTTGAT TCTGCTCTTA CTCTTGCCCC 30

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

GTAATAGAAC CAAAGGGCTG AGAC 24

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

GTTTCTTCGG AGTCAGACCT TACATTGTTG AG 32

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

ATCTCCCTGC TACCCACCTT 20

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

GTTTCTTGTT TTCAGTGAGT TTCTGTTGGG 30

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

GTGTGCCAAA CAACATTTGC 20

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

GTTTCTTCAA GCCATCAAGC TAGAGTGG 28

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

GGGCTTTTAA ACCCTTATTT AACC 24

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

GTTTCTTAGG TGATCTCAGA GCCACTCA 28

(2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

AGGGCAGGTG GGAACTTACT 20

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

GTTTCTTTGG AGTCAGTTGA GCTTTCTACC 30

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

TGAACTTGCC TACCTCCCAG 20

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

GTTTCTTAGC ATATATCCTT ACACAAGCAC A 31

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

CATGGTTCCA AAGGCAAGTT 20

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

GTTTCTTTTG AGGCTGAATG AGCTGTG 27

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

ACAGGTGGGA AGACTGAATG TC 22

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

GTTTCTTGCA GTACACATCA CATGACCTTG 30

(2) INFORMATION FOR SEQ ID NO:196:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

GAAATAGGCG GAAACTGGTT C 21

(2) INFORMATION FOR SEQ ID NO:197:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

GTTTCTTCGT TGTGGTTGTT CAGAAAGG 28

(2) INFORMATION FOR SEQ ID NO:198:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

GGTCAAGTGT TCAGAACGCA TC 22

(2) INFORMATION FOR SEQ ID NO:199:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

GTTTCTTGCA GGGATTATGC TAGGTCTGTA G 31

(2) INFORMATION FOR SEQ ID NO:200:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

AGCACTTCTG AGGAAGGGAC AC 22

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

GTTTCTTAGG GCAGGCAGAC ATACAAAC 28

(2) INFORMATION FOR SEQ ID NO:202:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

GCCAATGTGT TCCTAGAGCG AC 22

(2) INFORMATION FOR SEQ ID NO:203:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

GTTTCTTTTA AAGGGGGTAG GGTGTCACC 29

(2) INFORMATION FOR SEQ ID NO:204:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:

GGAAGGGAAA AGGACAAGGT TTTG 24

(2) INFORMATION FOR SEQ ID NO:205:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:

GTTTCTTAGC AAGAGCACTG GTGTAGGAGT C 31

(2) INFORMATION FOR SEQ ID NO:206:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:

GCTTTTCAAG CACTTGTCTC 20

(2) INFORMATION FOR SEQ ID NO:207:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:

TGGGATTGTG ACTTACCATG 20

(2) INFORMATION FOR SEQ ID NO:208:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

ACTTGGTGTC TTATAGAAAG GTG 23

(2) INFORMATION FOR SEQ ID NO:209:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

GTTTCTTAGC TGTGTTTGCT GCATC 25

(2) INFORMATION FOR SEQ ID NO:210:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

AGATGTGTGA TGAGATGCAG 20

(2) INFORMATION FOR SEQ ID NO:211:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:

GTTTCTTCAA ATAGTGCAAC AAACCC 26

(2) INFORMATION FOR SEQ ID NO:212:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:

TGTCATTCTG AAAGTGCTTC C 21

(2) INFORMATION FOR SEQ ID NO:213:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:

GTTTCTTCTG TAACTAACGA TCTGTAGTGG TG 32

(2) INFORMATION FOR SEQ ID NO:214:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

TATCAAGGTA ATATAGTAGC CACGG 25

(2) INFORMATION FOR SEQ ID NO:215:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

AGGTCTTTCA TGCAGAGTGG 20

(2) INFORMATION FOR SEQ ID NO:216:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

ATTGCCAAAA CTTGGAAGC 19

(2) INFORMATION FOR SEQ ID NO:217:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:

AGGTGACATA TCAAGACCCT G 21

(2) INFORMATION FOR SEQ ID NO:218:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:

TTGTCAACGA AGCCCAC 17

(2) INFORMATION FOR SEQ ID NO:219:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:

GTTTCTTGCA AGATTGTGTG TATGGATG 28

(2) INFORMATION FOR SEQ ID NO:220:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:

GCTCTCTATG TGTTTGGGTG 20

(2) INFORMATION FOR SEQ ID NO:221:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:

AAGAGTACGC TAGTGGATGG 20

(2) INFORMATION FOR SEQ ID NO:222:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:

TCCATTAGAC CCAGAAAGG 19

(2) INFORMATION FOR SEQ ID NO:223:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:

GTTTCTTCAC CAGGCTGAGA TGTTACT 27

(2) INFORMATION FOR SEQ ID NO:224:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

AATCGTTCCT TATCAGGTAA TTTGG 25

(2) INFORMATION FOR SEQ ID NO:225:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

GTTTCTTCAA AGAAAGCAAT TCCATCATAA CA 32

(2) INFORMATION FOR SEQ ID NO:226:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

GCATTTGTTG AAGCAAGCGG 20

(2) INFORMATION FOR SEQ ID NO:227:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:

CTTTGTTCCT TGGCTGATGG 20

(2) INFORMATION FOR SEQ ID NO:228:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:228:

AATAGTACCA GACACACGTG 20

(2) INFORMATION FOR SEQ ID NO:229:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:229:

CAATGGTTCA CAGCCCTTTT 20

(2) INFORMATION FOR SEQ ID NO:230:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:230:

AGCCTGGGAG ACAGAGTGAG 20

(2) INFORMATION FOR SEQ ID NO:231:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:231:

GTTTCTTGCA CTTTTTGGGG AAGGTG 26

(2) INFORMATION FOR SEQ ID NO:232:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:232:

GTTCCTCCCT TCCCTCTCC 19

(2) INFORMATION FOR SEQ ID NO:233:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:233:

GTTTCTTTCA GGGACTGGAT TGTAG 25

(2) INFORMATION FOR SEQ ID NO:234:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:

GTGTTCTTTA TGTGTAGTTC 20

(2) INFORMATION FOR SEQ ID NO:235:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:235:

GTTTCTTGGC AACAGAGTGA GACTCA 26

(2) INFORMATION FOR SEQ ID NO:236:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:

GTGACATCCA GTGTTGGGAG 20

(2) INFORMATION FOR SEQ ID NO:237:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:

GTTTCTTCCT AAGCAAGCAA GCAATCA 27

(2) INFORMATION FOR SEQ ID NO:238:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:

AAAGGCAATT GGTGGACA 18

(2) INFORMATION FOR SEQ ID NO:239:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:

GTTTCTTTTC AATCCTTGAT GCAAAGT 27

(2) INFORMATION FOR SEQ ID NO:240:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:

GGTGACAGAG CAAGATTTCG 20

(2) INFORMATION FOR SEQ ID NO:241:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:241:

GTTTCTTGTA GAGTTGAGGG AGCAGC 26

(2) INFORMATION FOR SEQ ID NO:242:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:242:

CATCCATCTC ATCCCATCAT 20

(2) INFORMATION FOR SEQ ID NO:243:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:243:

GTTTCTTTTC ACCCTACTGC CAACTTC 27

(2) INFORMATION FOR SEQ ID NO:244:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:244:

CCGCCATTTT AGAGAGCATA 20

(2) INFORMATION FOR SEQ ID NO:245:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:245:

GTTTCTTTTC TGGGACAATT GGTAGGA 27

(2) INFORMATION FOR SEQ ID NO:246:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:246:

TTTGTGTTAT TATTTCAGGT GC 22

(2) INFORMATION FOR SEQ ID NO:247:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:247:

GTTTCTTGTT TTTTGTTTCA GTTTAGGAAC 30

(2) INFORMATION FOR SEQ ID NO:248:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:248:

CATACCCAAA TCGTTCTCTT CCTC 24

(2) INFORMATION FOR SEQ ID NO:249:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:249:

GTTTCTTGGA AAAGCAAAGG CATCGTAGAG 30

(2) INFORMATION FOR SEQ ID NO:250:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:250:

TACTAACCAA AAGAGTTGGG G 21

(2) INFORMATION FOR SEQ ID NO:251:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:251:

CTATCATTCA GAAAATGTTG GC 22

(2) INFORMATION FOR SEQ ID NO:252:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:252:

GTATGGCAGT AGAGGGCATG 20

(2) INFORMATION FOR SEQ ID NO:253:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:253:

AAGGTTACAT TTCAAGAAAT AAAGT 25

(2) INFORMATION FOR SEQ ID NO:254:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:254:

CTGTTCAGGC CTCAATATAT ACC 23

(2) INFORMATION FOR SEQ ID NO:255:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:255:

AAGAGGATAG GTGGGGTTTG 20

(2) INFORMATION FOR SEQ ID NO:256:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:

CCTCCCACCT AGACACAAT 19

(2) INFORMATION FOR SEQ ID NO:257:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:

ATATGATCTT TGCATCCCTG 20

(2) INFORMATION FOR SEQ ID NO:258:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:

AAGAAAGACC TGGAAGGAAT 20

(2) INFORMATION FOR SEQ ID NO:259:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259:

AAACAGCAAA ACCTCATCTC 20

(2) INFORMATION FOR SEQ ID NO:260:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:260:

CCACCACTTA TTACCTGCAT 20

(2) INFORMATION FOR SEQ ID NO:261:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:261:

TGAATGAATG AATGAACGAA 20

(2) INFORMATION FOR SEQ ID NO:262:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:

AACTGTGATT GTGCCACTGC ACTC 24

(2) INFORMATION FOR SEQ ID NO:263:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:263:

GTTTCTTCAC CGCCTTTATC CCTCAAATG 29

(2) INFORMATION FOR SEQ ID NO:264:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:264:

GATGGGTGGA GGGCAGTTAA AG 22

(2) INFORMATION FOR SEQ ID NO:265:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:265:

GTCAAGCAAC TTGTCCAAGG CTAC 24

(2) INFORMATION FOR SEQ ID NO:266:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:266:

CAGGCTATCA GTTTCCTTTG GAG 23

(2) INFORMATION FOR SEQ ID NO:267:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:267:

GGCAGGTAAT ACTGGAGAAT TAGG 24

(2) INFORMATION FOR SEQ ID NO:268:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:268:

GACGGATCTC AGAGCCACTC 20

(2) INFORMATION FOR SEQ ID NO:269:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:269:

GTTTCTTAAA AGATAAGGGC TTTTAAACC 29

(2) INFORMATION FOR SEQ ID NO:270:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:270:

AGTTTCACAG CTTGTTATGG 20

(2) INFORMATION FOR SEQ ID NO:271:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:271:

GGTTGATGAA GTGAGACTTT 20

(2) INFORMATION FOR SEQ ID NO:272:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:272:

ATGGTGGATG CATCCTGTG 19

(2) INFORMATION FOR SEQ ID NO:273:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:273:

GTTTCTTGTA TTGACTCCTC CTCTGC 26

(2) INFORMATION FOR SEQ ID NO:274:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:274:

CAGTAAACAT 10

(2) INFORMATION FOR SEQ ID NO:275:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:275:

TGTTGAGTGG 10

(2) INFORMATION FOR SEQ ID NO:276:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:276:

TCTCCTCAAT GTGCATGT 18

(2) INFORMATION FOR SEQ ID NO:277:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:277:

ATTCTACATA 10

(2) INFORMATION FOR SEQ ID NO:278:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:278:

GTGTTTGCAT 10

(2) INFORMATION FOR SEQ ID NO:279:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:279:

ACAAGTTGGC 10

(2) INFORMATION FOR SEQ ID NO:280:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:280:

TAGTACCAGA 10

(2) INFORMATION FOR SEQ ID NO:281:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:281:

TACATCCAAG AAAA 14

(2) INFORMATION FOR SEQ ID NO:282:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:282:

GAGACTCTGA CAAATATATA TA 22

(2) INFORMATION FOR SEQ ID NO:283:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:283:

TGTTGATCGC CAAACCAAAA TC 22

(2) INFORMATION FOR SEQ ID NO:284:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:284:

AATGCATGTA TGTATATGGT GTGGTATGTG TACATATG 38

(2) INFORMATION FOR SEQ ID NO:285:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:285:

CCTCCCAGAA CAATCATGAT AA 22

(2) INFORMATION FOR SEQ ID NO:286:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:286:

AGACAGTCTC AAAAAATATT TTAAAGAAAA AGCTGGATAA ATAACTAGCT TTAAGAAAAT 60
AAGAAGAAAA AGAAAGAAGA AAGTAA 86

(2) INFORMATION FOR SEQ ID NO:287:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:287:

AACTAGCTTT AAGAAAATAA GAAGAAAAAG AAAGAAGAAA GTAAGAAAGA GAAAGAAAAG 60
AAAGAAAAGA AAGAGGAATG ATTGAC 86

(2) INFORMATION FOR SEQ ID NO:288:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:288:

CGCGCACATA CACCCTTTCT CT 22

(2) INFORMATION FOR SEQ ID NO:289:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:289:

CAGTAAACAT CATGTTGAGT GG 22

(2) INFORMATION FOR SEQ ID NO:290:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:290:

TCTCCTCAAT GTGCATGTGT GCATGAGTGC ACATTCTACA TA 42

(2) INFORMATION FOR SEQ ID NO:291:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:291:

GTGTTTGCAT GTTGTACAAG TTGGC 25

(2) INFORMATION FOR SEQ ID NO:292:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:292:

TAGTACCAGA CACGTGCAGG CAAGCGCACC ATACATCCAA GAAAA 45

(2) INFORMATION FOR SEQ ID NO:293:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:293:

GGAGGCTGAG CAGGGGTGCC 20

(2) INFORMATION FOR SEQ ID NO:294:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:294:

ACTCCCACAG GTACCTGCAG 20

(2) INFORMATION FOR SEQ ID NO:295:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:295:

CTGCCCTCAC GTAAGCGCCT 20

(2) INFORMATION FOR SEQ ID NO:296:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:296:

GCTGTTGCAG GGTAATGTTG 20

(2) INFORMATION FOR SEQ ID NO:297:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:297:

CATCAGACAG GTGCGTACA 19

(2) INFORMATION FOR SEQ ID NO:298:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:298:

GGCTGGTGAG GAGGGGCTGA 20

(2) INFORMATION FOR SEQ ID NO:299:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:299:

CGCTCTGTGG GTGAGCTTCA 20

(2) INFORMATION FOR SEQ ID NO:300:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:300:

TGTGGAATAG CCCAATTACA 20

(2) INFORMATION FOR SEQ ID NO:301:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:301:

AGGGTGCTGA GTGAGTAGTA 20

(2) INFORMATION FOR SEQ ID NO:302:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:302:

TTCTTTTCAG GCCCTCGTGT 20

(2) INFORMATION FOR SEQ ID NO:303:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:303:

TGCTGACCCG GTATGGTGGT 20

(2) INFORMATION FOR SEQ ID NO:304:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:304:

TTTGGTGCAG CCTGTGACTC 20

(2) INFORMATION FOR SEQ ID NO:305:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:305:

CGCACACAAG GTCAGTGTTC 20

(2) INFORMATION FOR SEQ ID NO:306:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:306:

TCTTTCCCAG GTTACTCCTT 20

(2) INFORMATION FOR SEQ ID NO:307:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:307:

ATCAAAGACT GTAAGTAACC 20

(2) INFORMATION FOR SEQ ID NO:308:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:308:

TCTATTTCAG ATGCTGATTC 20

(2) INFORMATION FOR SEQ ID NO:309:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:309:

AGTAGAACAA GTAAGTGCAG 20

(2) INFORMATION FOR SEQ ID NO:310:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:310:

TTTTCAAAAG GCCTCCAAAG 20

(2) INFORMATION FOR SEQ ID NO:311:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:311:

GAGCCCTGAG GTAAGTTAAT 20

(2) INFORMATION FOR SEQ ID NO:312:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:312:

GCTTTTTCAG ATACTACTAT 20

(2) INFORMATION FOR SEQ ID NO:313:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:313:

TAACATGTTC AACTGTCTGT 20

(2) INFORMATION FOR SEQ ID NO:314:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:314:

TGTTATATGC ATTTATCTTC 20

(2) INFORMATION FOR SEQ ID NO:315:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:315:

GGTAAATGAG GTAAGTCCTG 20

(2) INFORMATION FOR SEQ ID NO:316:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:316:

TCTTGTTAAG ATCGCTCTCT 20

(2) INFORMATION FOR SEQ ID NO:317:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:317:

CCTTGCCCAG GTTCTCTTAA 20

(2) INFORMATION FOR SEQ ID NO:318:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:318:

GCAATCGCAC CTGCACACCC 20

(2) INFORMATION FOR SEQ ID NO:319:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:319:

ACTGCCCATT TCTGGTAAAG 20

(2) INFORMATION FOR SEQ ID NO:320:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:320:

CCCCTAACAG ATCATGATTC 20

(2) INFORMATION FOR SEQ ID NO:321:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:321:

ACGTGCAATG GTAAGAGGGC 20

(2) INFORMATION FOR SEQ ID NO:322:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:322:

TGTTTTGCAG TTTCCAGTGG 20

(2) INFORMATION FOR SEQ ID NO:323:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:323:

AAGTGGAACG GTGACTCTCT 20

(2) INFORMATION FOR SEQ ID NO:324:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:324:

TCCTTCACAG GCCAGTGCAG 20

(2) INFORMATION FOR SEQ ID NO:325:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:325:

GAACAAACTG GTGAGTAGTA 20

(2) INFORMATION FOR SEQ ID NO:326:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:326:

TTTTTTGTAG AGCCTTCCAT 20

(2) INFORMATION FOR SEQ ID NO:327:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:327:

AGCACAGTAG GTAACTAACT 20

(2) INFORMATION FOR SEQ ID NO:328:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:328:

ATGGCCACAG ATTTGTTGGA 20

(2) INFORMATION FOR SEQ ID NO:329:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:329:

CTTCCTGTTG GTAAGCTGTC 20

(2) INFORMATION FOR SEQ ID NO:330:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:330:

TTCTCCTTAG CAGAGTCACC 20

(2) INFORMATION FOR SEQ ID NO:331:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:331:

AAAAAGCACA GTAAGTTGGC 20

(2) INFORMATION FOR SEQ ID NO:332:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:332:

TTTTCATCAG ACCCGAGAGG 20

(2) INFORMATION FOR SEQ ID NO:333:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:333:

GAGCTATGAG GTGAGGAGTT 20

(2) INFORMATION FOR SEQ ID NO:334:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:334:

TTTGTTACAG ATATTACTAC 20

(2) INFORMATION FOR SEQ ID NO:335:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:335:

AGCCTGGAAA TGCGTGTTTC 20

(2) INFORMATION FOR SEQ ID NO:336:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:336:

CGAGAATTCA CTCGAGCATC AGG 23

(2) INFORMATION FOR SEQ ID NO:337:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:337:

CCTGATGCTC GAGTGAATTC T 21

(2) INFORMATION FOR SEQ ID NO:338:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 848 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...848
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:338:

```
ATG ATT CTG GAA GGA AGT GGT GTA ATG AAT CTC AAC CCA GCC AAC AAC      48
Met Ile Leu Glu Gly Ser Gly Val Met Asn Leu Asn Pro Ala Asn Asn
 1               5                  10                  15

CTC CTT CAC CAG CAA CCA GCC TGG CCG GAC AGC TAC CCC ACA TGC AAT      96
Leu Leu His Gln Gln Pro Ala Trp Pro Asp Ser Tyr Pro Thr Cys Asn
            20                  25                  30

GTT TCC AGC GGT TTT TTT GGA AGC CAG TGG CAT GAA ATC CAC CCT CAG     144
Val Ser Ser Gly Phe Phe Gly Ser Gln Trp His Glu Ile His Pro Gln
        35                  40                  45

TAC TGG ACC AAA TAC CAG GTG TGG GAA TGG CTG CAG CAC CTC CTG GAC     192
Tyr Trp Thr Lys Tyr Gln Val Trp Glu Trp Leu Gln His Leu Leu Asp
    50                  55                  60

ACC AAC CAG CTA GAC GCT AGC TGC ATC CCT TTC CAG GAG TTC GAC ATT     240
Thr Asn Gln Leu Asp Ala Ser Cys Ile Pro Phe Gln Glu Phe Asp Ile
65                  70                  75                  80

AGC GGA GAA CAC CTG TGC AGC ATG AGT CTG CAG GAG TTC ACG AGG GCA     288
Ser Gly Glu His Leu Cys Ser Met Ser Leu Gln Glu Phe Thr Arg Ala
                85                  90                  95

GCA GGC TCA GCT GGG CAG CTG CTC TAC AGC AAC CTA CAG CAT CTC AAG     336
Ala Gly Ser Ala Gly Gln Leu Leu Tyr Ser Asn Leu Gln His Leu Lys
            100                 105                 110

TGG AAC GGC CAA TGC AGC AGT GAC CTT TTC CAG TCC GCA CAC AAT GTC     384
Trp Asn Gly Gln Cys Ser Ser Asp Leu Phe Gln Ser Ala His Asn Val
        115                 120                 125

ATT GTC AAG ACT GAA CAA ACC GAT CCT TCC ATC ATG AAC ACA TGG AAA     432
Ile Val Lys Thr Glu Gln Thr Asp Pro Ser Ile Met Asn Thr Trp Lys
    130                 135                 140

GAA GAA AAC TAT CTC TAT GAT CCC AGC TAT GGT AGC ACA GTA GAT CTG     480
Glu Glu Asn Tyr Leu Tyr Asp Pro Ser Tyr Gly Ser Thr Val Asp Leu
145                 150                 155                 160
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TTG GAC AGT AAG ACT TTC TGC CGG GCT CAG ATC TCC ATG ACA ACC TCC 528
Leu Asp Ser Lys Thr Phe Cys Arg Ala Gln Ile Ser Met Thr Thr Ser
165 170 175

AGT CAC CTT CCA GTT GCA GAG TCA CCT GAT ATG AAA AAG GAG CAA GAC 576
Ser His Leu Pro Val Ala Glu Ser Pro Asp Met Lys Lys Glu Gln Asp
180 185 190

CAC CCT GTA AAG TCC CAC ACC AAA AAG CAC AAC CCA AGA GGC ACT CAC 624
His Pro Val Lys Ser His Thr Lys Lys His Asn Pro Arg Gly Thr His
195 200 205

TTA TGG GAG TTC ATC CGA GAC ATT CTC TTG AGC CCA GAC AAG AAC CCA 672
Leu Trp Glu Phe Ile Arg Asp Ile Leu Leu Ser Pro Asp Lys Asn Pro
210 215 220

GGG CTG ATC AAA TGG GAA GAC CGT TCG GAA GGC ATC TTC AGG TTC CTG 720
Gly Leu Ile Lys Trp Glu Asp Arg Ser Glu Gly Ile Phe Arg Phe Leu
225 230 235 240

AAG TCA GAA GCT GTG GCT CAG CTG TGG GGG AAA AAG AAA AAT AAC AGT 768
Lys Ser Glu Ala Val Ala Gln Leu Trp Gly Lys Lys Lys Asn Asn Ser
245 250 255

AGC ATG ACA TAC GAG AAG CTC AGC CGG GCT ATG AGA TAT TAC TAC AAA 816
Ser Met Thr Tyr Glu Lys Leu Ser Arg Ala Met Arg Tyr Tyr Tyr Lys
260 265 270

CGA GAA ATC CTG GAA CGT GTG GAT GGA CGA CG 848
Arg Glu Ile Leu Glu Arg Val Asp Gly Arg Arg
275 280

(2) INFORMATION FOR SEQ ID NO:339:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 283 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:339:

Met Ile Leu Glu Gly Ser Gly Val Met Asn Leu Asn Pro Ala Asn Asn
1 5 10 15
Leu Leu His Gln Gln Pro Ala Trp Pro Asp Ser Tyr Pro Thr Cys Asn
20 25 30
Val Ser Ser Gly Phe Phe Gly Ser Gln Trp His Glu Ile His Pro Gln
35 40 45
Tyr Trp Thr Lys Tyr Gln Val Trp Glu Trp Leu Gln His Leu Leu Asp
50 55 60
Thr Asn Gln Leu Asp Ala Ser Cys Ile Pro Phe Gln Glu Phe Asp Ile
65 70 75 80
Ser Gly Glu His Leu Cys Ser Met Ser Leu Gln Glu Phe Thr Arg Ala

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                85                  90                  95
Ala Gly Ser Ala Gly Gln Leu Leu Tyr Ser Asn Leu Gln His Leu Lys
            100                 105                 110
Trp Asn Gly Gln Cys Ser Ser Asp Leu Phe Gln Ser Ala His Asn Val
        115                 120                 125
Ile Val Lys Thr Glu Gln Thr Asp Pro Ser Ile Met Asn Thr Trp Lys
    130                 135                 140
Glu Glu Asn Tyr Leu Tyr Asp Pro Ser Tyr Gly Ser Thr Val Asp Leu
145                 150                 155                     160
Leu Asp Ser Lys Thr Phe Cys Arg Ala Gln Ile Ser Met Thr Thr Ser
                165                 170                 175
Ser His Leu Pro Val Ala Glu Ser Pro Asp Met Lys Lys Glu Gln Asp
            180                 185                 190
His Pro Val Lys Ser His Thr Lys Lys His Asn Pro Arg Gly Thr His
        195                 200                 205
Leu Trp Glu Phe Ile Arg Asp Ile Leu Leu Ser Pro Asp Lys Asn Pro
    210                 215                 220
Gly Leu Ile Lys Trp Glu Asp Arg Ser Glu Gly Ile Phe Arg Phe Leu
225                 230                 235                     240
Lys Ser Glu Ala Val Ala Gln Leu Trp Gly Lys Lys Lys Asn Asn Ser
                245                 250                 255
Ser Met Thr Tyr Glu Lys Leu Ser Arg Ala Met Arg Tyr Tyr Tyr Lys
            260                 265                 270
Arg Glu Ile Leu Glu Arg Val Asp Gly Arg Arg
        275                 280
```

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising a sequence within a mammalian ASTH1 locus, or a polymorphic variant thereof.

2. An isolated nucleic acid molecule according to Claim 1, wherein said nucleic acid molecule encodes an ASTH1 polypeptide.

3. An isolated nucleic acid molecule according to Claim 1 wherein said nucleic acid comprises a promoter or regulatory region.

4. An isolated nucleic acid molecule according to Claim 1 comprising a probe for detection of an *ASTH1* locus polymorphism.

5. An array of oligonucleotides comprising:
two or more probes according to Claim 4.

6. An isolated nucleic acid comprising a microsatellite repeat associated with a predisposition to asthma.

7. A nucleic acid according to any of claim 1 to 5, wherein said ASTH1 locus is human.

8. A cell comprising a nucleic acid composition according to any of claims 1 to 4.

9. A purified polypeptide composition comprising at least 50 weight % of the protein present as the product of the nucleic acid of Claim 1.

10. A method for detecting a predisposition to asthma in an individual, the method comprising:
analyzing the genomic DNA or mRNA of said individual for the presence of at least one predisposing *ASTH1* locus polymorphism or a sequence linked to a

predisposing polymorphism; wherein the presence of said predisposing polymorphism is indicative of an increased susceptibility to asthma.

11. A method according to Claim 10, wherein said analyzing step comprises detection of specific binding between the genomic DNA or mRNA of said individual with a probe or probes according to either of Claims 4 or 5.

12. A method according to Claim 10, wherein said analyzing step comprises detection of specific binding between the genomic DNA or mRNA of said individual with a microsatellite marker listed in Table 1.

13. A non-human transgenic animal model for *ASTH1* gene function comprising one of:

(a) a knockout of an *ASTH1* gene;

(b) an exogenous and stably transmitted mammalian *ASTH1* gene sequence; or

(c) an *ASTH1* promoter sequence operably linked to a reporter gene.

14. A method of screening for biologically active agents that modulate ASTH1 function, the method comprising:

combining a candidate biologically active agent with any one of:

(a) a mammalian ASTH1 polypeptide;

(b) a cell comprising a nucleic acid encoding a mammalian ASTH1 polypeptide; or

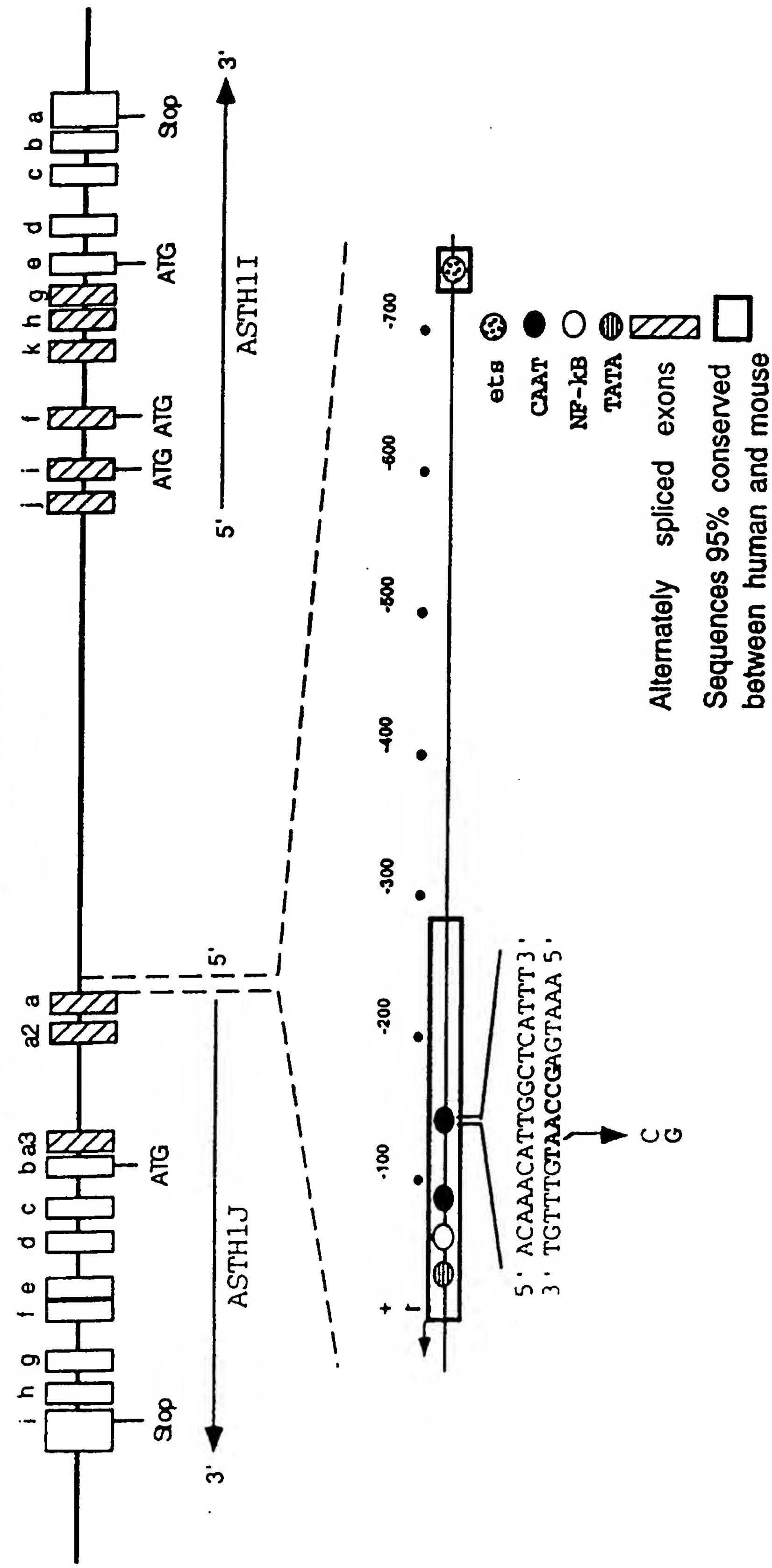
(c) a non-human transgenic animal model for ASTH1 gene function comprising one of: (i) a knockout of an *ASTH1* gene; (ii) an exogenous and stably transmitted mammalian *ASTH1* gene sequence; or (iii) an *ASTH1* promoter sequence operably linked to a reporter gene; and

determining the effect of said agent on ASTH1 function.

15. An isolated nucleic acid that hybridizes under stringent conditions to any one of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, or SEQ ID NO:328.

16. An isolated nucleic acid that encodes a polypeptide or fragment thereof having an amino acid sequence substantially identical to the sequence as set forth within any one of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:339.

FIGURE 1: GENOMIC STRUCTURE OF THE ASTH1I AND ASTH1J GENES



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/01260

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12Q 1/68
US CL :435/6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SANDFORD et al. Localisation of atopy and β subunit of high-affinity IgE receptor (FcεRI) on chromosome 11q. The Lancet. 06 February 1993, Vol. 341, pages 332-334, see entire article.	1-14
Y	GERHARD et al. Isolation of 1001 New Markers from Human Chromosome 11, Excluding the Region of 11p13-p15.5, and Their Sublocalization by a New Series of Radiation-Reduced Somatic Cell Hybrids. Genomics. 1992, Vol. 13, pages 1133-1142, see entire article.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 APRIL 1998	18 MAY 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
EGGERTON CAMPBELL
Telephone No. (703) 308-0196